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### Volume 15, Bibliographical references

In the following references, for *J. Physiol.* read

*J. physiol. (Paris)*:

page 324, reference 2; page 325, references 22, 23; page 326, references 42, 47.

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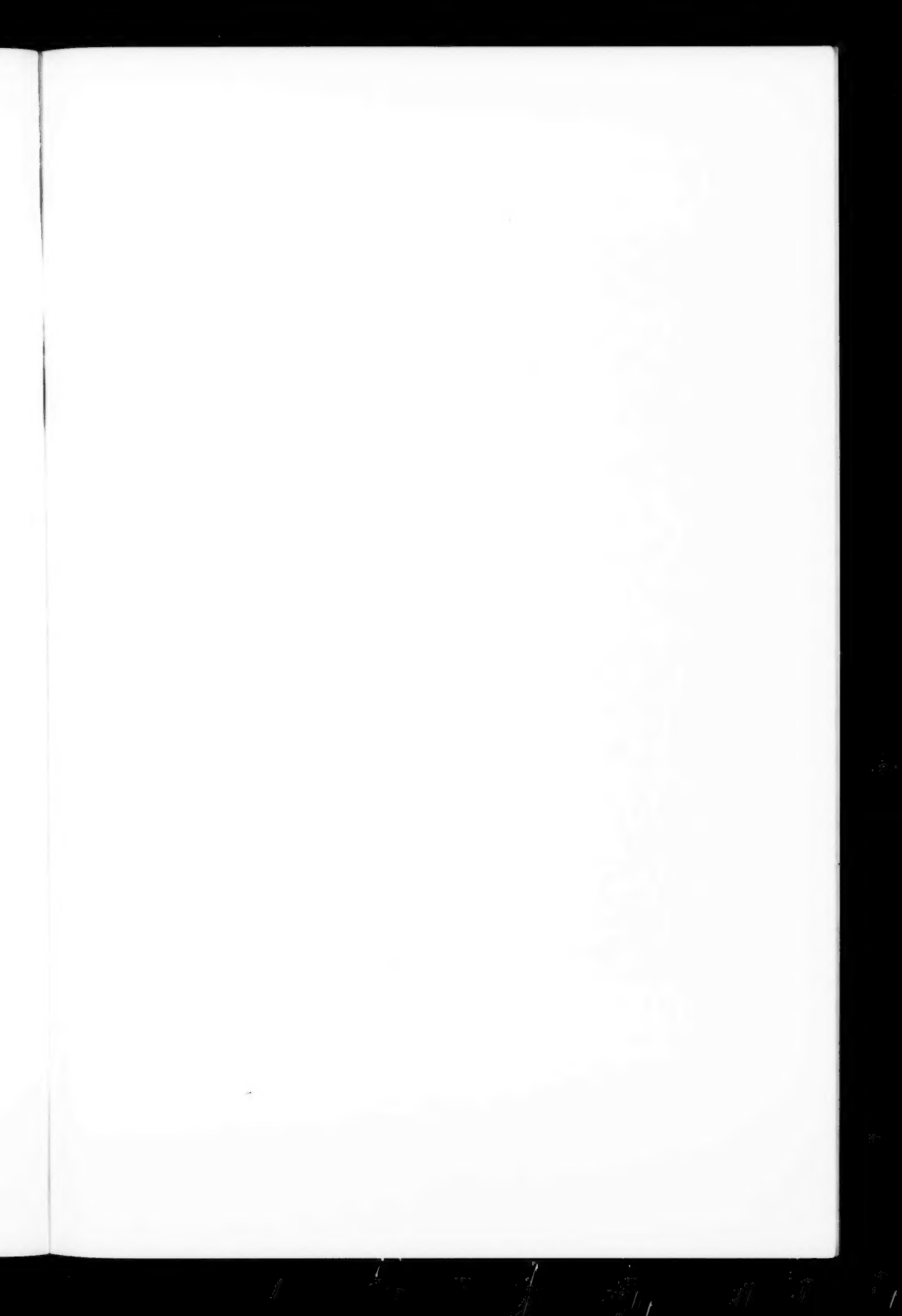
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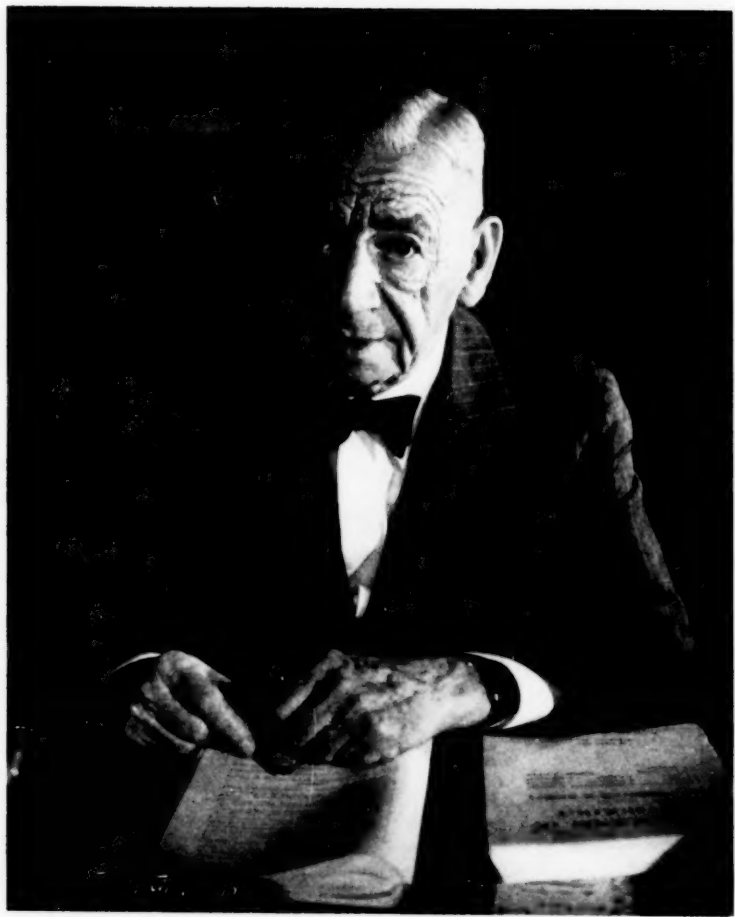
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OTTO LOEWI, M.D., PH.D.



## PREFATORY CHAPTER

### REFLECTIONS ON THE STUDY OF PHYSIOLOGY

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A scientific worker nowadays rarely finds it possible to publish papers which have a personal touch. If this rare opportunity occurs, he can discuss the origin and the development of his problem, show the way eventually found to solve it, draw conclusions even of hypothetical character from the results obtained and hint at their possible implications. By this means the reader becomes acquainted at least in part with the author's scientific personality. In general, such revelations are not found in the ordinary papers which fill the scientific journals. As a rule, they contain a short introduction, detailed reports on the methods and experiments and such conclusions as can be safely drawn from them. Usually the style too is impersonal. Characteristic of this is the lack of "I" and "we" in current literature.

Reviewers also frequently restrict themselves to compiling the data contained in papers in a purely factual, encyclopedic fashion. It looks as though such reviewers were afraid to add anything of their own: criticism, interpretation or subordination of isolated facts to general concepts.

This routine form of publication is perfectly appropriate for the information of scientists familiar with the fields concerned. It is doubtful, however, whether the merely factual content of papers, unless their importance is self-evident, helps much to inspire and educate students. As in all branches of life, interest in human achievements is much increased if one is somewhat acquainted with the personality behind them. Mere information about methods and facts does not contribute much to training beginners in scientific thinking and in the art of research. I have repeatedly asked young students of biology what kind of papers they prefer to read. Let me quote literally one of the answers characteristic of most of them. "For me the most exciting papers are those which describe exactly what the individual scientist experienced from the beginning to the end of his experiments, the mistakes he made and how he learned through them what the answers were."

This reaction indicates that the aim of personal education coexists with that of information. The more usual mode of publication may have come as a consequence of the large bulk of papers submitted to editors. This in its turn may be partly due to the pressure to publish fragments of research in order not to lose support of one kind or another. Yet a way could be found to comply with the demand for some personal character in papers provided one considers, as I do, that this is an important stimulus for study.

Up to about the second decade of our century, there was no rushing and timing of research, and the length of publications was restricted only in ex-

ceptional cases. Consequently many "exciting" papers were published and quite frequently they proved to have a decisive influence upon young readers. In fact this was true for myself. The reading of Gaskell's paper "On the Rhythm of the Heart of the Frog and of the Nature of the Action of the Vagus Nerve" (1) and of Miescher's paper on "The Biology of the Rhine Salmon" (2) directed my interest toward basic science. This may be the reason why ever since I have had a high regard for the inspiring and educational value of papers of the past. Among them for me, besides those just quoted, are "Diabetes Mellitus after Extirpation of the Pancreas" by Minkowski (3), "Studies on Tetanus" by Meyer & Ransom (4), and "The Action of Adrenaline" by Elliott (5).

I refer to these papers here not because of the highly important discoveries they contain—for that a review would suffice—but for the particular lines of thought by which the discoveries came about. These thoughts can be grasped only by reading the original papers. All of them were conceived by imaginative, inquiring minds, probing into the very roots of the problems and approaching them from many different angles. I have such a high regard for the inspiring and educational value of these papers that I used to request every student to read them before he began to work with me on a special problem. Obviously I do not pretend that my favorite papers are the best of all, nor that the idea of recommending papers of the past as sources of inspiration and education is a new one.

Far greater than the influence of printed matter has always been that of great figures in science, who at the same time were great teachers. Such persons were able to attract highly gifted students, who in their turn augmented their heritage and frequently became leaders in science in their own right. For special reasons, which shall be given later, I should like to illustrate this with several examples, recalling the most eminent students of three great figures who taught in the golden era of physiology in the nineteenth century.

Among Johannes Mueller's pupils were the physiologists von Bruecke, Dubois-Reymond, Helmholtz and Pflueger; the anatomists Henle and Schwann; the histologist von Koelliker, the experimental pathologist Traube and the pathologist Virchow. Among Carl Ludwig's almost innumerable pupils were the physiologists Bohr, Bowditch, Fick, Flechsig, Gaskell, von Kries, Kronecker, Kuehne, Luciani, Mosso, Pavlov and Tigerstedt, the experimental pathologist Cohnheim, and such biochemists and pharmacologists as Abel, Miescher and Schmiedeberg. Sir Michael Foster, who in contrast to Mueller and Ludwig added very little to our knowledge through his own research, was the founder of the greatest school of physiologists and biologists in England. Among his pupils were the physiologists Gaskell, Langley and Sherrington, the neurologist Henry Head, the embryologist Balfour, the zoologist Marshall, the animal morphologist Sidgwick and the plant morphologist Darwin.

Johannes Mueller, Carl Ludwig and Sir Michael Foster, according to all

biographical data, shared to the highest degree the qualities of contagious enthusiasm, broadmindedness and imagination, humility and deep devotion to their pupils. These are qualities which in themselves suffice to attract outstanding students. I refer, however, to these figures because they attracted and educated students who later devoted their lives not just to physiology, but to other branches of science. This was made possible only because through the mode of their education in physiology the students were made familiar with principles which, transcending the boundaries of the special field, applied to many other realms of experimental science. Besides the art of experimenting and observing, they learned the ways of thinking required by science. They learned how to select the object to be explored, how to interpret and evaluate the results obtained, and how to integrate them into the whole body of knowledge. In this way students were not only made familiar with methods and facts, but were imbued with that general scientific spirit which shapes the pattern of the true scholar and investigator. They received the kind of education which in a seemingly paradoxical fashion is defined in that profound sentence: "Education is what remains when you have forgotten all the facts you ever learned."

This kind of education can be acquired only if students have the opportunity to come into close association with their masters. The great masters amply provided this and thereby fulfilled a fundamental condition for the establishment of "schools"—trends of thought. It is important to add that the teaching by the masters was not restricted to research students, but was extended through formal lectures to all medical students. Lecturing was in general not regarded as a burden but as a privilege. In my own opinion, there is nothing more gratifying than to convey ones own ideas about things to young people and in this way to stimulate their thinking.

It has been a common experience that in each period the interest of scientists tends to concentrate on particular branches of science to the neglect of others. A frequent reason is that achievements in one field become overshadowed by fundamental discoveries in other fields which promise important developments. Many physiologists at medical schools within the last twenty years have been disturbed by the fact that students have been less and less attracted to the domain of medical physiology.<sup>1</sup> It seems worthwhile to search for factors—other than economic ones—which may be responsible for this.

For one thing medical physiology has had to share its research interests with the clinic. For a long time the clinic has increasingly participated in and contributed to progress in physiology. Think, for example, of such clinicians as Addison, Graves, Kocher, Magnus-Levy, Minkowski, Cushing, Hench, all of them pioneers in the field of internal secretion. There is every reason to believe that the clinic will continue to attract students who are interested in experimental medicine, including physiology. From a nondepartmental

<sup>1</sup> This term, in general, is used synonymously with: classical, special, official, departmental, human, mammalian, and organ physiology.

point of view it obviously makes little difference where the light comes from.

Another reason for the decline in the number of students in the departments of physiology may be the following: During the nineteenth century most of the fundamental problems in organ physiology which could be approached by the methods available were solved. Consequently fewer fundamental discoveries could be made during the next decades. Wiggers (6) formulated the same viewpoint with regard to the consequences of the achievements of the great masters in the following beautiful way:

Through their genius and zeal the virgin soils yielded bountiful harvests. Indeed, so great had been the crop of discoveries that those of us who entered fields of investigation early in the twentieth century felt that the law of diminishing returns must operate until the soil could be refertilized or until better tools should become available.

It was therefore perhaps natural that one began to attempt the more detailed analysis of more or less known functions. For this purpose refined, specific methods frequently were needed and developed. Many of them were extremely complicated and long training was necessary to become familiar with them. It appears that these circumstances, together with an apparently general tendency of our time to worship methods and gadgets, has quite frequently placed emphasis on technical procedures, and diverted interest away from physiological problems. This has gone so far that sometimes one has the impression that in contrast with former times, when one searched for methods in order to solve a problem, frequently nowadays workers look for problems with which they can exploit some special technique.<sup>2</sup>

It goes without saying that new methods, elaborated in order to approach a definite problem, often have led to the solution of many other problems. It is also true, however, that most discoveries have emerged primarily from ideas starting from observed facts. Working hypotheses should not be mistaken for preconceived ideas. As J. J. Thomson said: "A scientific idea is a tool and not a creed." Since such terms as "hypothesis" or—even more so—"speculation" are taboo for many scientists, I should like to quote the following sentence from Baldwin's preface to "Dynamic Aspects of Biochemistry" (8): "Speculation plays and has always played an important part in the advancement of scientific knowledge; for no research worker gropes blindly after he knows not what; he invariably begins with certain reasonable possibilities in mind. In short, he speculates." I cannot refrain from quoting in this connection also part of a letter of Miescher (9) written to the pharmacologist Boehm in 1876. I hope that the reader will be as interested in his view of the speculative process as I have been for more than fifty years.

<sup>2</sup> A somewhat similar development became predominant also in pharmacology. It was originally defined as the science aiming at the exploration of vital processes through the study of changes in them produced by chemicals. In 1946, however, Welch & Bueding (7) wrote: "Emphasis has shifted to an exhaustive study of each drug, so that all its multitudinous effects might be uncovered, rather than to a continued study of functions and the manner in which they are influenced by chemical substances."

In order to begin exploration of an uncharted scientific field, in which there is a lack even of the bare elements for posing clear-cut questions, a unique type of imaginative power seems necessary. This can be designated as the building of mental bridges. It consists of the visualization of the main elements of the design based solely upon a few dimly indicated building stones. Out of these elements the imaginative scientist makes the first draft of the building plan. He arrives at it not so much out of logical necessity, as out of an artistic feeling of esthetic harmony. Further study of such a plan of a whole field, however dim the outlines may be, will clearly indicate at what point the actual work should begin. The drive to think in such a fashion and the ability to do so may often be found in individuals of otherwise mediocre attainments. In them it may easily lead to delusion, when they do not appreciate that this first sketch is only the preliminary step to an exact understanding and that it should be erased once its purpose as a guide has been accomplished. It is, in my opinion, a malady of present physiology that the method of preliminary synthetic thinking is coming into disrepute and that its application by the rising generation is intentionally suppressed.

This discussion may be concluded with a contemporary statement by Professor Landis of Harvard University (10). Referring to the view of Howard Mumford Jones of the same institution deploring the increasing tendency to train scientists predominantly as superb research technicians in a narrow field, to the neglect of their broader development as carriers of a flame in a philosophic and pedagogic sense, he says, "In physiology particularly specialization and emphasis on technology must be balanced by recognizing the value of some philosophy within the science."

Philosophy, I suppose, signifies in this connection an attitude towards the meaning and aim of physiology. It doubtless is lack of such a philosophy that often leads to the overestimation of the importance of isolated facts as opposed to ideas, as well as of quantity as against quality. Facts are likely to be meaningless if they result from research which starts not from a basic concept but from such reasoning as: "Nobody else seems to have done it so far" or "What else can I do with my method?" In fact, the choice of a subject should comply with the demands concisely formulated by Weiss (11):

The primary aim of research must not be just more facts, but more facts of strategic value. By strategic value I mean that property of an observation or experiment that leads to the clarification or solution of a problem, to deeper insight into a phenomenon, to the linking of previously unrelated facts and ideas or simply to the birth of a new problem; at any rate leads to some end other than the bewildered question "So what?"

To comply with such demands, imaginative minds are indispensable. They may remain latent unless they get a chance to become manifest, for instance by seeing or performing experiments. This at the same time can be a stimulus to scientific curiosity which, in turn, may create the drive and enthusiasm for a lifetime of research. For the development of an imaginative mind and the eventual realization of its potentialities, favorable conditions must be established. In my view the most important of these conditions is an inspiring apprenticeship, which guides the student early into independent research.

After this second deviation let us return to the point at issue: the attitude of our young generation towards human physiology. This is the fundamental medical science, as its knowledge is indispensable for understanding disturbed functions in disease. Human physiology comprises in the main the study of general and specific functions of organs and organ systems. The ultimate mechanisms underlying the organ functions are still little understood. They depend on the properties of the cells, the smallest functional units of organs as of practically all living organisms.

It certainly has been due to the recognition by human physiologists of the basic value of studies on cells that for many decades they have used single cells—often, for instance, red cells—in order to learn not only about their specific properties but also about cellular properties in general. It appears to be the consequence of a normal development that nowadays students are particularly interested in properties and functions of cells. It may be partly for this reason that one of the fields of organ physiology which attracts students today at least as much as it ever did is that of the function of nerves. This study, increasingly conducted on single fibres, promises that we may gain a better insight at the same time into such fundamental phenomena as permeability, resistance, irritability, excitation and inhibition, as well as into the conduction and transmission of stimuli. The results obtainable by the study of nerves can in principle be applied to a much broader area. The particular part played by the nerve as a subject of research originates, in my opinion, from the fact that the axons are cytoplasmic processes of single cells and allow detailed studies on the cellular level. In this connection also the ever-increasing number of studies of single muscle fibres has to be mentioned. These studies yield information not only on specific muscle functions but also on contractility in general. The study of other organs also will certainly attract students, if ways are found to approach them on the cellular level.

There exists such an approach toward the study of the chemical properties and functions (metabolism) of many cells. In fact, within the past decades interest has been concentrated more and more on biochemistry. Many fundamental and inspiring discoveries have been made in this field and their pursuit has seemed so promising that highly qualified young workers in ever increasing numbers have turned to biochemistry, and to such branches of biology as cytology, microbiology (including chemotherapy and virology) and genetics, in which essential cellular problems can be approached by the application of chemical methods.

It seems appropriate to discuss here the relation of biochemistry, at its present state of development, to physiology. Biochemistry has by now developed into an almost autonomous science. According to Hopkins (12), "the ultimate aim of biochemistry should be an adequate and acceptable description of molecular dynamics in living cells and tissues." In so saying Hopkins emphasized the biological viewpoint. In order to approach this goal, one has to start with the isolation and analysis of individual substrates, cofactors and enzymes as well as with the study of the mechanism and inter-

relation of their activities. The greatest part of this work is done not with intact cells or tissues, but with extracts, homogenates and cell particles. Studies of this kind conducted on the molecular level can reveal chemical mechanisms which probably operate *in vivo*. Such information is of great significance not only for the chemist but also for the biologist. From a biological point of view, however, it must be integrated with studies on the intact cell.

Because of the harmonious interrelation of the complex chemical events *in vivo*, which is disrupted by destruction of the cellular organization, the full significance of *in vitro* findings depends on whether they can be verified *in vivo*. Even in this case, the *in vitro* findings inform us only of basic chemical tools which may serve the chemical functions of cells, tissues and organisms. They do not solve the purely physiological problem of the function itself, which consists in the use by the cell of the tools according to its needs. The functions of the cell depend on its organization and on the regulation of its activities on behalf of the whole. Extremely little is known about these things.

Physiology conceived in the broadest sense has to include the study of functions on different levels of organization. Progress on one level can be made independently of that on other levels. Which one is preferred depends on the sphere of interest of the individual scientist and this in its turn on the scientific climate of the period. Which level is chosen for study does not matter as long as the unity of the organization as a whole, resulting from the integration of the interrelated, interdependent and interacting functions, receives proper emphasis.

An impressive proof of the correctness of the view that progress can be made on one level independently of that on other levels is the marvellous development of human physiology. The accumulation of a vast knowledge of organ functions, their conditions and interrelations as well as their integration into the whole of the organism is almost entirely due to studies on the organ level. In fact, the knowledge acquired on this level of organization by now has reached the point at which human physiology, in order to inspire and to recruit a sufficient number of able students for its future progress, should comply with their ever-growing desire to deepen their insight into the ultimate mechanisms underlying organ functions. These mechanisms are inherent in the cells. A knowledge of the properties of cells is essential for understanding the mechanisms and hence for interpreting the various vital processes. For this reason medical physiology should expand the scope of its interest more than in the past to cellular physiology.

This segment of physiology, which like biochemistry in the last few years has developed to an almost autonomous discipline, includes a great part of what is called general physiology. There does not exist a uniform, clearcut definition of this science; accordingly the selection and treatment of the material differs to a certain extent in various textbooks.

According to the broadest concept the final goal of general physiology is the elucidation of the basic principles of the life processes. As it is certainly true that all living things are fundamentally alike, general physiology has to



search for unifying principles and characters common to all of them [Heilbrunn (13)]. For this reason general physiology, as was pointed out long ago by Claude Bernard (14) who introduced the term, has to study the properties of organized matter and to explain the processes and the mechanisms of vital phenomena just as physics and chemistry explain the processes and mechanisms of inanimate phenomena. Bernard also specified to a certain extent the subject and the direction of the studies he had in mind when he defined general physiology as the study of the physicochemical properties of the cell and its environment, beyond this of the physicochemical relations between cell and environment, and most generally of phenomena common to animals and plants (15). He (16) and later Bayliss (17) considered "general physiology" to be the foundation of physiology, particularly of medical physiology, which both designated as "applied physiology."<sup>3</sup>

There certainly are medical physiologists who devote research and part of their teaching to cellular or general physiology. On the whole, however these subjects do not appear prominently enough in medical physiology.<sup>4</sup> In current textbooks of mammalian physiology one finds scarcely any reference to problems, principles or even fundamental findings in these fields. It is significant also that meetings of medical and general physiologists are held separately.

DuBois (18) has not been the only one to express great concern about the future of medical physiology, because of the increasing schisms which have split off essential parts of the subject. Among the factors responsible for this may have been the neglect of subjects which appear to have only a remote usefulness for medicine. Certainly cellular physiology is not remote, since in disease medicine often has to face disturbed functions of cells, the understanding of which depends on our state of knowledge of the mechanism and the conditions of normal cell function.

Be that as it may. The concentration on organ functions at all events means a considerable narrowing of the scope of education in physiology. The basis of education in any field, however, can never be broad enough if we insist on progress. It seems appropriate, if not indeed necessary, to discontinue at least the separation of human and general (cellular) physiology in its

<sup>3</sup> "Physiology being the science of life is to be regarded as an autonomous and independent study to be cultivated for its own sake and not merely for its application for the practice of medicine" [Claude Bernard (16)]. "Principles of general physiology might be of service to all desiring a general, elementary treatment of what may be called 'Abstract physiology,' as distinct from the 'applied physiology,' required by the agricultural, medical or veterinary student for the purpose of his profession" [Bayliss (17)].

<sup>4</sup> This shortcoming has recently been stressed in a remarkable paper by Anderson (19) who pleaded for supplementing human physiology by "microphysiology." With this he had in mind the description of the functional properties of cells that are significant in the physiology of the whole animal, as well as the explanation of those properties in terms of cellular components down to molecular dimensions.



present fairly rigid form, and instead to secure some kind of unification.<sup>5</sup> The opportunity should be offered to medical students to become more familiar with problems, principles and the accumulated findings in the field of general (cellular) physiology. Whoever has experienced the enduring and stimulating influence of Bayliss' "Principles of General Physiology,"<sup>6</sup> particularly on medical students with their natural interest in the question "What is Life?", will share my confidence that the proposed unification will help in recruiting more students of the kind physiology needs for its progress. In any case, their horizon will be broadened. This effect, particularly nowadays, cannot be overestimated, as it will help to protect students against the danger of too early specialization in a restricted field of physiology.

The question, of course, will immediately be raised whether the time available for teaching medical physiology suffices to include some cellular physiology. Teaching cannot and should not try to cover all the facts known in a field. It should transmit to the students only a selection which obviously depends more or less on the individuality of the teacher and his particular interests. If a teacher does not aim at competing—in regard to completeness of any chapter—with a textbook or even a monograph, and yet is convinced of the essential value of general (cellular) physiology for the students' education, he certainly will be able to include it and indeed begin with it in his teaching.

In conclusion I should like to add a few words, which represent a kind of personal confession.

Physiology deals with the study of the functions serving the maintenance and reproduction of living organisms. The only tools, mechanisms and arrangements, which are needed for the achievement of those functions and which can be studied, are physicochemical in nature. Living organisms are not only able to preserve themselves under normal conditions by using preformed regulatory arrangements but can meet even strong interference from within or from without by their capacity to adapt themselves or to repair damage. It is questionable whether we will ever understand the basis of the tendency toward and capacity for self-preservation. It seems indeed as if this tendency and capacity were manifestations of a directed, innate creative power of living organisms, not accessible to physicochemical analysis as interpreted at present.

This limitation, if real, of our present and perhaps future knowledge should not bother us. Robert Louis Stevenson's saying, "To travel hopefully

<sup>5</sup> The "Annual Review of Physiology" may be regarded as a pioneering product of this viewpoint since about one third of its reviews are devoted to subjects of general or cellular physiology.

<sup>6</sup> Many facts presented in this unique book obviously are out of date. It nevertheless still makes stimulating and exciting reading and for fundamental principles and historical perspective nothing has yet taken its place. I wonder whether one should not recommend it strongly as a classical, historical book. Also as such it will raise enthusiasm and stimulate thinking.

is a better thing than to arrive," holds true also for the attitude of the scientist. Experience has informed us that even a scientist's firm conviction that he is unable to reach the final goal does not in the least interfere with his ardent drive to explore. This originates from his belief in the meaningfulness of the universe as manifested in its orderly regularity. This aspect of reality provokes his admiration and awe. From admiration and awe arises a feeling which, in my opinion, can only be defined as religious. It shows that the scientist follows a drive, not only of his mind, but of his spirit. Einstein, to whom nature seems to have revealed more of her secrets than to any other man of our time, calls this cosmic religious experience the strongest and noblest mainspring of scientific research.

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# PHYSICAL PROPERTIES OF PROTOPLASM<sup>1</sup>

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The scope of this subject is considerable if fundamental physical properties such as size and form down to the molecular level are also considered in relationship to a metabolic pattern or other biological phenomena. The space available obviously limits the possibility of dealing with the greater part of the relevant data, to say nothing of the reviewer's inability to cover the whole field, the main interest is therefore focused on the nucleus and cytoplasm, and the review covers the period from approximately July 1952 to June, 1953.

## CHROMOSOMES AND NUCLEUS

The physical properties and structural organization of the chromosomes are still far from clear. Quantitative polarization microscopy and other optical measurements have provided information about birefringence and refraction in living cells [Pfeiffer (1 to 4), Inoué (5, 6); see also Hughes (7)]. Pfeiffer (8, 9, 10) made photoelectric recordings of the anisotropy of *Drosophila* salivary chromosomes. He found that stretching of the chromosomes up to 20 to 30 per cent of their original length only influenced the interband spaces which are positively birefringent, whereas the bands were not influenced. With greater stretching the interband became increasingly positively birefringent, leaving, however, the band spaces negatively anisotropic. Pfeiffer stated that this phenomenon is due to the inability of the components of the chromosomes, the polypeptide chains and nucleoproteins, to increase their orientation further. Pfeiffer (8) also made refractometric determinations of the protoplasm of various cells in mitosis, using the Becke line-imbibition method. The cell substance showed maximal values at the beginning of metaphase and at the end of anaphase. Evidence of a parallel orientation of the protein components in intermitotic *Tradescantia* microspores was obtained (10). Rheodichroism, flow birefringence, and double refraction in protoplasm in relation to ultramicroscopic particles have been discussed by Pfeiffer (11) and by Seifriz (12).

Studies have been made on the spindle with respect to both ultrastructure and chemical composition. The validity of earlier data has been reviewed by Swann (13). Measurements of the total birefringence of mitotic apparatus in various cells by Pfeiffer (14) afforded new evidence that the spindle consists of a system of elongate particles arranged lengthwise. In Pfeiffer's opinion, the streaming movements play an important role in initiating the formation

<sup>1</sup> The following abbreviations are used in this chapter: RNA (ribonucleic acid); DNA (deoxyribonucleic acid); ATP (adenosinetriphosphate); PNA (pentosenucleic acid); LP (Lotmar-Picken).

of the mitotic apparatus. Using a refined technique, Inoué (6) found that the fibres of the spindle are composed of gel fibrils, whose micelles are preferentially oriented and weakly interlinked; their birefringence increases with stretching and diminishes with contraction. The formation of spindles in unfertilized egg cells has been observed by Dan, Ito & Mazia (15). The change in birefringence during division was studied by Inoué (6), Inoué & Dan (15a), and by Swann (13, 16). Swann (13) measured retardation curves for the living spindles of sea urchin eggs and calculated the coefficient of birefringence at different points within the mitotic figures. A low coefficient of birefringence was found in the centrosome, rising to a maximum at  $5\ \mu$  from the centre, and then falling rapidly to a minimum at the equator. It was concluded that the spindle either is orientated throughout, with a varying degree of orientation, or consists of discrete fibrils radiating from the centres. In *Chaetopterus* eggs, Inoué [see Swann (13)] found spindle strands of stronger birefringence running from the centrioles to the chromosomes, possibly caused by the grouping of numerous fibres into bundles. Colchicine and low temperature [Inoué (17, 18)] were found reversibly to destroy the orientation of the spindle micelles. Mazia & Dan (19) succeeded in isolating the mitotic apparatus from dividing sea urchin eggs. Its nucleic acid content, apart from the chromosomal elements, was extremely low or zero. The protein isolated accounted for about 2 per cent of the protein of the egg. A critical survey of our present knowledge of the dynamics of the spindle has been made by Swann (13, 16).

Measurements of chromosomes from *Chironomus*, using x-ray micro-radiography, showed that the dry weight per volume unit seems to be 2 to 10 times higher in the bands than in the interband spaces (Engstrom & Ruch (20)).

Nucleoli from starfish oocytes were isolated and chemically investigated by Vincent (21). The RNA<sup>1</sup> content was found to be 2.2 to 4.6 per cent of the dry weight and to differ in composition from that of the cytoplasm. It is to be noted that no histone or histidine could be found. A phosphoprotein is thought to form the structural basis of the nucleolus of the starfish oocytes.

Stern (22) discussed the physicochemical organization of the nucleus and the chromosomes and the principle of variation and permutation necessary for a supposed chromosome function. Summing up the present state of knowledge, Stern stated that the gene is a biological conception without chemical analogy. Watson & Crick (23, 24) presented a new hypothesis for the gene, on the supposition that the structure of DNA<sup>1</sup> consists of two coiled chains providing the molecular bases of a template needed for genetic replication, in which the sequence of bases is the code which carries the genetic information. Pontecorvo (25) discussed the definition of the gene and emphasized that, contrary to the conception of the chemical composition of the chromosome as static, it is more than possible that this composition varies under different conditions. The results of Mirsky and co-workers (26, 27, 28) have a direct bearing on this problem. The uptake of glycine-N<sup>15</sup> was found to be more rapid in nuclei from tissues with a high metabolic rate. In

the chromosome the uptake of  $N^{15}$  into DNA was low, into histone higher, and into residual protein still higher, comparable with that into the cytoplasmic protein.  $P^{32}$  was shown to be incorporated into the nuclei of *Tradescantia* and *Lilium* during a short period of the interphase [Taylor (29)]. The incorporation of  $P^{32}$  and  $C^{14}$  into the nucleic acids was more rapid in the liver cell nucleus than in the cytoplasm [Smellie & McIndoe (30)].

Electron microscopy has hitherto added little to our knowledge of the chromosomes. Prophase and telophase chromosomes of onion root tip cells appear to have a fibrillar structure which is not visible at metaphase and anaphase [Rosza & Wyckoff (31)]. Chromosomes from oocytes of *Triturus* have been shown to consist of single axial, 200 Å wide, filaments with loops attached at intervals along their length [Tomlin & Callan (32)]. The presence of thin, cylindrical structures, often coiled about each other, has been demonstrated [van Winkel *et al.* (33), Hielweil *et al.* (34)]. These twisted tubules are thought to be enclosed in a casing. In erythrocyte nuclei, two types of chromosomes are described by Yasuzumi *et al.* (35). This finding is disputed by Houwink (36).

In the discussion on the identity of "isolated chromosomes" there now seems to be conclusive evidence that the structures studied are actually chromatin threads [Ris & Mirsky (37), Denués (38, 39, 40)]. On the other hand, a pertinent question is whether the data obtained correspond to the conditions *in vivo*. In the isolation of nuclei solvents are used, and in studies on microscopical sections some sort of fixation is applied, both types of treatment causing a loss of material. In enzyme studies on isolated nuclei, Mirsky and co-workers took the precaution of using a water-free treatment to prevent loss of water-soluble substances. It may be mentioned that ordinary fixation solutions cause a loss of material, especially in the nucleus [Brattgård and Hydén (41), Hydén (42)]. Bernstein & Mazia (43), on the basis of analyses of DNA from sea urchin sperm, concluded that the composition of whole nuclei differs from that of the chromosomal substance.

The evidence for the constancy of the DNA content of each set of chromosomes in the various cells of an organism has been summarized and new evidence presented [Mirsky & Ris (44), Mazia (45), Brachet (46), Thomson *et al.* (47)]. In the sea urchin, the DNA content of the egg does not seem to be the same as that of the sperm. Using a microbiological method, it was found that the DNA content of the former was about 20 to 25 times that of the latter [Elson & Chargaff (48)]. An explanation of this exception to the rule may be that in some species all of the DNA in the egg is not localized to the nucleus, but some is present in the cytoplasm [Schrader (49), Hoff-Jørgensen & Zeuthen (50)].

In adult tissue, the average amount of DNA per nucleus is uninfluenced by any sort of treatment provided that it does not lead to destruction [Thomson *et al.* (47)]. Thus, it remains constant in the liver despite marked changes in the chemical composition and cytological picture. PNA is found in varying amounts in the liver cell nucleus and decreases during starvation.

Zbarski & Perivozikova (51) reported the presence of a complex nuclear protein-containing histone with contractile properties and discussed its possible importance for mitosis.

Although present in considerable amounts, the lipids of the nucleus have generally been neglected. An account of earlier data is given by Mazia (45). Tyrell & Richter (52) found 25 to 30 per cent lipids in isolated nerve cell nuclei. In nuclei from the liver and thymus, the lipids were found to be firmly bound to the protein; and electrophoretic study showed the presence of one component, a lipoprotein with an isoelectric point between pH 4.65 and 4.85 [Carver & Thomas (53); Wang, Mayer & Thomas (54)]. A globulin has been isolated from mammalian nuclei; when studied by electrophoresis, it was found to be a single component and to have the characteristics of euglobulin [Kirkham & Thomas (55)]. A lipoprotein similar to that of cellular nuclei and a histone-like protein have been removed from mammalian sperms; this left the head smaller, but unchanged in shape. These small head-like residual structures are composed entirely of DNA. A possible explanation for the arrangement of this substance is that the histone-like protein forms a layer inside the layer of lipoprotein and outside the bulk of DNA ([Dallam & Thomas (56)]).

*Mitosis.*—A comprehensive discussion of the present knowledge of the mitotic cycle from physical, chemical, structural, and functional aspects is presented by Hughes (7). Rather than attempt to construct a general synthesis of mitosis, the author confined himself to scrutinizing the data available, thus giving the reader food for thought. Swann (16) and Mitchison (57) put forward a theory that relates mitosis with cleavage. They suggested that the decrease in birefringence of the mitotic apparatus, starting when the chromosomes begin to separate, is brought about by the release from the chromosomes of a catalytic agent; the cortical changes at cleavage would also be caused by this process. They also postulated a controlling cycle for the mitotic process and presented physical and chemical evidence of cyclic processes reversing at metaphase and interphase. Mitchison (57) reported evidence leading to the conception of a new cell membrane model, characterized by positive form and negative intrinsic birefringence, greater thickness than earlier supposed, and a looped protein structure. Such a membrane would actively expand in area under the influence of the catalytic agent, which diffuses out towards the poles of the cell, resulting in cell division. Heilbrunn (58, 59) discussed agents causing stimulation or prevention of cell mitosis. Protoplasmic clotting is believed to produce mitotic gelation which results in a mitotic spindle and division.

Ultraviolet microspectrographic analyses have been made both on mitotic cells *in vitro* and on living cell nuclei [Davies (60), Walker & Yates (61)]. It was found in tissue cultures that the material in the cell nuclei absorbing at 2600 Å doubles during interphase. It was concluded that DNA is synthesized during interphase and that additional absorbing molecules may include DNA precursors. In *Drosophila* salivary chromosomes, there seemed

to be a direct correlation between DNA content and nuclear volume. The results indicated that the mature double salivary chromosome contains about 1000 strands [Kurnick & Herskowitz (62)]. The DNA content of salivary gland cells from *Helix* seems to vary as much as from 1 to 30 [Leuchtenberger & Schrader (63)]. As the size of a nucleus and its DNA content decreased, the amount of secretion in the cytoplasm increased.

The validity of data obtained with microspectrophotometric methods has been much debated. There seems to be a general tendency to interpret with caution quantitative data obtained in this way. The advantages and errors of microspectrophotometric methods are discussed by Davies & Walker (64), Frazer & Davidson (65), Danielli (66), and Brattgård & Hydén (143).

Important viewpoints on the genetic mechanism are obtained from studies on the transforming agent of bacteria. The isolation of nucleic acid from pneumococcus type VI led to the belief that the nucleic acid exists in the cells as free acid and that the protein-nucleic acid bond is very weak. Koenig *et al.* (67) and Zamenhof *et al.* (68) purified and separated electrophoretically the DNA of *Haemophilus influenzae* possessing transforming activity. They found no decrease in this activity with preceding purification; on the contrary, electrophoretic separation seemed to yield more active DNA.

Fox and Goodman (69) studied the effect of a series of cytosine nucleosides on the developing chick embryo; they found that glucopyranosylcytosine hydrochloride produced inhibition of morphogenesis and differentiation, presumably by a competitive mechanism. Thomas *et al.* (70) were unable to confirm the observation by Mazia (71) that homologous DNA exerts an inhibitory action on the development of amphibian eggs.

#### THE CYTOPLASM

Polarization microscope studies on inclusions in the microspores of *Tradescantia* showed a high degree of positive anisotropy as well as an oriented organization [Pfeiffer (72), and Swann & Mitchison (73)]. Using a cryoscopic method, the osmotic pressure of sea urchin eggs and muscle fibres has been measured [Potts (74)].

New techniques have now made it possible to study such fundamental properties as cell mass and intracellular concentrations. The method for intracellular mass determinations [Engström & Lindström (75)] is based on the fact that the mass of the biological material with regard to C, N, and O, representing the main components of cells, is proportional to the absorption of the x-rays within the 8 to 12 Å wave-length region. Using sections from fixed material, Nürnberger *et al.* (76) found that the fixed nerve cell cytoplasm contained about 35 per cent dry substance and the parietal cells of the gastric mucosa about 15 per cent [Engström & Malmström (77)]. The ratio of the weight of the chief cells to that of the parietal cells was found to be about 2:1. In order to reduce the relatively large errors of the x-ray method and to make it possible to carry out quantitative measurements, refinements have been made. The method has also been adapted for use in connection



with extraction and digestion of nerve cell material. When fresh, frozen material was used, the fixation procedure was observed to cause considerable loss of material from the cells, especially from the nucleus. The values for the amount of dry substance in fresh, frozen cells are therefore considerably higher than those obtained from fixed material. Thus, in the former case, the figure was found to be about 50 per cent, as compared to 30 per cent for fixed nerve cells of the same type [Brattgård & Hydén (41), Brattgård (78), Brattgård & Hallén (79), Hallén & Ingelstam (80), Hydén (81), Brattgård *et al.* (82)].

Another method for the determination of mass and concentration in living cell organisms has been elaborated [Barer (83 to 87)] Barer & Ross (88), Barer *et al.* (89), Davies & Wilkins (90). The refractive index of the object is determined by the immersion method, using a suitable plasma albumin preparation in a water or saline solution. Barer found that the refractive index of the cytoplasm of snail spermatocytes and amoebocytes corresponded to a content of about 14 per cent of solids and of bacteria amounting to between 25 and 40 per cent. The advantage of this method is its simplicity and the accuracy with which the refractive index match can be made, since the eye is particularly sensitive to amplitude changes.

Holter *et al.* (91) devised a method for separating cell particles according to their density. They found a density of 1.10 to 1.20 for isolated mitochondria and of 1.25 to 1.30 for microsomes.

The rheo-dichroism has been studied in fibroblasts from tissue culture [Pfeiffer (92)]. With an increased fluid velocity, an increase was noted in the value of the rheo-dichroism, indicating a straightening out of the fibrillar units, the "leptones" of the protoplasm.

The tissue culture technique has proved its usefulness as a means of studying fundamental cell problems. In a stimulating paper, Weiss & Garber (93) outlined a way of replacing static cell morphology by quantitative morphology. They gave examples in a study on fibroblasts in tissue culture, expressing the cell characteristics on a quantitative scale. Rhythmic pulsatile movements of glia cells from brain tissue cultures have been recorded by means of time-lapse cinematography [Pomerat (94)]. On the basis of further experiments, evidence was presented of the existence of both interstitial movements produced along the processes of astrocytes, and of intraneuronal fluid movements produced along the processes of astrocytes, and of intraneuronal fluid movements in the oligodendroglia cells. The implication of these findings for the conception of neuronal metabolism was also discussed [Pomerat (95)].

Using a perfusing chamber, it is possible to observe behavioural changes of cells with the introduction of various substances, such as antigens. In the course of this work nuclear rotations have been observed [Pomerat (96)].

Neugebauer (97) presented a biophysical theory on the autocatalytic formation of protein in the protoplasm. Further evidence of a relationship between metabolism and morphogenetic processes was brought forward by



Hultin (98). He found that, in the sea urchin, the incorporation rate of  $N^{15}$  into pyrimidines and purines from the low-molecular and RNA fractions rapidly accelerated during the blastula formation and culminated during the mesenchyme blastula stage.

*Mitochondria.*—An extensive and critical survey of the physical and chemical properties of mitochondria and microsomes is given by Lindberg & Ernster (99). The mitochondria consist of a solid core and a liquid phase, the whole being surrounded by a selective, permeable lipoprotein membrane. Both types of particle have a high lipid content. The mitochondria contain all the iron porphyrin respiratory enzyme of the cell, whereas the microsomes are bearers of the greater part of the cytoplasmic nucleic acid. The study of the enzymic organization of the mitochondria has led to the belief that these particles contain the apparatus used by the cell for the liberation of the energy of substrates, and its conversion into forms suitable for anabolic processes and the performance of work.

The mitochondria contain the entire mechanism whereby the energy liberated in these oxidations is fixed in the so-called energy-rich bonds. The energy from the primary substances containing such bonds is transferred reversibly by the mitochondrial system to ATP.<sup>1</sup> The function of this energy-transferring system is to activate the substances. By the concentration of respiratory and energy-transferring enzymes and coenzymes in the mitochondria, the cell achieves the maximum capacity of oxidation and energy transfer attainable with this complement.

The physical properties of mitochondria are also discussed by Lehninger (100), and by Zollinger (101). The latter especially studied these structures with the phase-contrast microscope. Levine & Chargaff (102) found that the lipids of mitochondria do not differ in chemical composition from those of the cell as a whole, although they differ in solubility. De Lamirande, Allard & Cantero (103) investigated electrophoretically the behaviour of the composition of soluble proteins in liver mitochondria under normal and abnormal stimulated growth. Berthet *et al.* (104) have shown in rat liver cells that an unspecific acid ester phosphatase is associated with more than 60 per cent of the mitochondria in a sucrose homogenate. The bound form of the enzyme is supposed to be that characteristic of the living, intact cell; it can be liberated by making the mitochondria permeable by treatment with surface-active substances of electrolytes and can then attack the substrate. Glycerophosphate, like sucrose, was shown to have a protective action on the mitochondrial structure, because of the fact that sucrose is capable of maintaining an effective osmotic pressure in the surrounding medium whereas sodium chloride, for example, is unable to do so. The results support the view that the mitochondria are surrounded by a membrane with selective permeability. A sedimentation study showed that the acid phosphatase belonged to a special kind of granules, having a low sedimentation rate by differing from microsomes [de Duve *et al.* (105)]. Cleland (106), using a light-scattering technique, studied heart mitochondria prepared in a medium con-

taining tetrasodium ethylenediaminetetraacetic acid (Versene), which binds calcium ions in a complex linkage. Quantitative values were obtained for the relative penetration rates of cations, anions, and nonelectrolytes. The permeability was shown to be dependent upon the concentration of calcium ions.

The liberation of energy from active mitochondria by means of added enzyme systems possibly takes place at the mitochondria surface [Lindberg & Ernster (99)]. It further seems that ATP and other energy-rich compounds can penetrate this surface only with difficulty. It has been suggested that the hexokinase reaction takes place at this site [Lindberg & Ernster (107)]. Peters (108) suggested that there is a permeability barrier to the penetration of citrate into the mitochondria. Crane & Sols (109) found glucokinase to be bound to the mitochondria fraction.

The mechanism of phosphorylative energy transfer in the mitochondria has been studied in relation to the hypothesis that the mechanism is controlled by kinase processes occurring in the cytoplasm [Lindberg & Ernster (107)]. The energy-transferring system of the mitochondria in relation to cell oxidation has also been discussed. The relationship between the shape of the mitochondria from heart muscle and oxidative activity was studied by Harman & Feigelson (110). The rod form is believed to allow only slow oxidation. This type can, under certain circumstances, be transformed into small granules situated between the fibrils. The intimate relation to the myofibrils suggests an active contribution to the contractile process [Harman & Feigelson (111)]. Osmotic concentration of the sucrose medium and its effect on the shape of heart mitochondria and oxidation and oxidative phosphorylation was also investigated by Harman & Feigelson (112). The secretory activity of mitochondria from the kidney was studied by Bartley & Davies (113). They found that these structures can support concentration differences of inorganic ions between themselves and the outer medium. The mitochondria are considered to be responsible for the maintenance of ion concentration gradients within the cell. In a study on muscle mitochondria, Lenicque (114) stated that the small type of mitochondria take part in the lipid metabolism, whereas the sarcosomes are arranged along the length of the fibrils and serve as the source of ATP for the contraction process. Sacktor (115) was, however, unable to obtain coupled phosphorylation with this material but found that the finely dispersed mitochondrial particles of the housefly have much greater adenosinetriphosphatase activity than intact mitochondria.

Further electron-microscopic studies have been made on mitochondria membranes. Sjöstrand (116) found an outer double membrane surrounding mitochondria obtained from the retinal rods and the excretory cells of the pancreas and the proximal convoluted tubules of the mouse kidney. The two single membranes were found to be 45 Å thick, the space between them being 70 Å. Transversely oriented double membranes were observed in the interior of the mitochondria; their spacing varied with the different types of cells studied. It was suggested that the double membrane represents two

membranes of protein character, separated by a double-layer of lipid molecules. Electron-microscope studies on mitochondria from red beet tissue also disclosed the existence of a membrane; its thickness was of the order of 270 Å. The changes in appearance of these mitochondria after treatment with solutions or with different osmotic pressure have been described [Farrant, Robertson & Wilkins (117)]. A comparative electron-microscopic study of the cytoplasmic structures of cultured adult embryonic and neoplastic epithelial cells has been made. It revealed the presence of submicroscopic particles in large quantities in all neoplastic-type cells cultured from human carcinomas. The density of the particles was higher than that of the mitochondria and their diameter smaller. No such particulates could be found in normal control cells [Cannan-Selby & Berger (118)].

Using phase-contrast microscopy, Zollinger (119) found support for the theory that microsomes can be transformed into mitochondria. New evidence has been presented by Lenicque (114) and by Eichenberger (120). In the regeneration of mitochondria in kidney tubules, small cytoplasmic particles first became enlarged by the deposition of protein. In a second stage a membrane was formed, after which the particle had the morphological appearance of a mitochondrion. During embryonic development, there is an exponential increase in respiration in the blastula stage of sea urchin embryos which is considered to be a direct function of mitochondriogenesis [Gustafson & Lenicque (121)]. The problem of mitochondria and melanization is discussed by Hesselbach (122).

The definition of the Golgi substance is still debated [Dalton & Felix (123), Trager (124), Lanham (125)].

Studies made with fluorescein-labelled antibodies to identify antigens within cells showed that antigenic molecules become concentrated in the connective tissue cells of all organs soon after intravenous injection. They are also present in hepatic cells, renal cells, and in the cells of the adrenal cortex, both in the nucleus and in the cytoplasm [Coons (126)].

Systems of double membranes have been observed in the cytoplasm of excretory cells of the mouse pancreas [Sjöstrand (127)]. The membranes were found to be oriented mainly parallel to the cell membrane, and the results were correlated with polarization optical analyses.

#### NUCLEO-CYTOPLASMIC INTERRELATIONSHIP

This is primarily a genetic and cell-physiological problem involving structural, physical, and chemical questions, and is thus too complicated to discuss in this short review. Since, however, considerable progress has been made, certain of its aspects will be briefly surveyed.

The problem does not consist only of such questions as the role of the nucleus in protein synthesis and the nuclear-governing effect on cytoplasmic constituents. It also includes the effect of the cytoplasm on the nucleus and the chromosomes.

The role of the nucleus in cell metabolism has been specially illustrated

by studies on unicellular organisms. Using enucleated fragments of amoebas, Brachet (128, 129) found that the oxidative consumption is on a normal level for about two weeks. When the regeneration of nucleated fragments was inhibited in *Acetabularia*, changes in the structure and composition of the nucleus ensued. It was concluded from the results that the nucleus is dependent upon the production of energy in the cytoplasm for the maintenance of both structure and composition. Incorporation of radioactive  $\text{CO}_2$  into the proteins of enucleated *Acetabularia* was found to be independent of the presence of the nucleus during the first two weeks after section of the alga. At that time, however, there was a decrease in protein synthesis in the absence of the nucleus. It could be demonstrated that the rapidity of the incorporation of  $\text{CO}_2$  into the proteins of the chloroplasts is at least twice as large as that into the proteins of the small cytoplasmic particles. This is contrary to the conditions in animal tissues [Brachet & Chantrenne (130), Vanderhaeghe (131)]. Enucleated fragments of *Acetabularia* were still able to synthesize catalase during the first days after sectioning, but this ability was lost in the course of two weeks. The results indicate that the nucleus governs the production of proteins in an indirect way [Chantrenne *et al.*, (132)]. The incorporation of  $\text{CO}_2$  into enucleated fragments of *Acetabularia* ceases in darkness. Using radioactive glycine, it was found that its incorporation into the protein was unaffected by illumination [Brachet & Brygier (133)]. Brachet (46) expressed the view that the synthesis of cytoplasmic RNA is dependent on the nucleus for its maintenance. The nucleus participates in the coupling between oxidation and phosphorylation by producing diffusible coenzymes necessary for these reactions to take place in the mitochondria [see also Steinert (134)]. The results of investigations on enzymes of isolated cell nuclei also substantiate this conclusion [Allfrey *et al.* (135), Stern *et al.* (136); see also the papers by Hogeboom & Schneider (137, 138, 139)]. On the other hand, in a discussion on nucleus-cytoplasm interaction, Mazia (45) stated that there is little evidence that the nucleus contributes significantly to the current activities of the cell, except on a long-term basis.

Using labelled phosphate to study the rate of nucleic acid cytoplasmic synthesis in *Polytomella*, Jeener (140, 141, 142) did not find the usual correlation between the amount of PNA<sup>1</sup> and the growth rate. His inference of an independent multiplication of smaller and larger cytoplasmic particles was disputed by Lindberg & Ernster (99).

Mirsky *et al.* (135, 136) studied experimentally whether the cytoplasm has an effect on the nucleus, and whether there is a reciprocal feed-back system, reflected in the differentiation of the nucleus. The localization of haemoglobin in the erythrocyte nucleus and of arginase and catalase in the liver cell nucleus, as well as comparative enzyme studies, indicated that differentiation is also a nuclear process. They also found evidence indicating that the nuclear composition varies with the age and the physiological state of the cell. The observation that large amounts of lipids are localized both in the nucleus and the cytoplasm of the nerve cell points in the same direction

[Hydén (81), Brattgård & Hydén (143)]. The problem has also been mentioned by Mazia (45) and Lindberg & Ernster (99).

#### RADIATION EFFECTS

An important methodologic achievement was made by Zirkle & Bloom (144). Using a microbeam of protons a few  $\mu$  in diameter from a Van de Graaff generator as the source of radiation and a microscopic system, they observed the effect on tissue culture cells of irradiation of a certain part of the single cell. Time-lapse photography was used for continuous study of the cell changes after irradiation with from 50 to 4000 roentgens. The preliminary findings included temporary and permanent chromosome and mitotic changes. A few dozen protons to the chromosomes produced abnormalities, but the extrachromosomal regions were unaffected even by several thousand protons. Small accessory nuclei were frequently produced.

In an extensive discussion on the mechanism of cell irradiation effects. Errera (145) focused particular interest on the changes in the nuclear DNA. He concluded that even moderate x-irradiation inhibits the new synthesis of this substance. The same author also studied the effect of ultraviolet irradiation on DNA (146, 147).

A number of aspects of radiation effects on cells are dealt with in the Symposium on Radiobiology, 1952 (148). The effect of irradiation on mitosis is discussed. The action of ultrasonics on mitosis and cell structure was investigated by Selman (149), Lepeschkin & Goldman (150), and Ackerman (151). Friedenwald & Sigelman (152) studied the inhibition of mitoses in corneal epithelium by ionization radiation. They stated the inhibition to be a result of the destruction of a substance produced at an exponentially steady rate during interphase. The effect of irradiation on cell growth, enzyme activity, nucleic acid content, nerve function, and ion permeability has been discussed by Geckler & Kimball (153), Sarachek & Townsend (154), Hirschfield & Giese (155), Glubrecht (156), Blum & Matthews (157), Freeman & Giese (158), Gärtner (159), Weiss (160), Dounce (161) Nachmansohn (162), Parpart & Green (163). The importance of  $H_2O_2$  formation in the irradiation effect is discussed by Barron, Seki & Johnson (164). They found that  $H_2O_2$ , despite its high oxidation-reduction potential, is a slowly acting oxidizing factor, inhibiting the metabolism in cells only in concentrations higher than those found after irradiation of biological systems with lethal doses of x-rays. They concluded that the formation of  $H_2O_2$  is of little importance in the mechanism of the irradiation effect. Other aspects of the mechanism of ionizing radiation on cells are dealt with by Barron & Flood (165) and Barron & Finkelstein (166). According to Bacq & Herve (167) the protecting effect of cysteine could not be related to the SH groups.

#### CELL MEMBRANES AND PERMEABILITY

The physicochemical aspects of biological membrane permeability and the properties of ionic membranes have been treated and reviewed by Teorell

(168) and by Ussing (169). The application of tracers in permeability studies is discussed by Ussing (170) and the structural factors involved, by Danielli (171). A survey of the relationship between cell surface and fertilization, mainly in sea urchins, was given by Runnström (172). Ross (173) presented evidence supporting the view that an effect of insulin is to increase the permeability of cell membranes to biologically important carbohydrates by accelerating the enzymic transport mechanism. Osterhout (174, 175, 176) entered into a thorough discussion of the mechanism of accumulation of substances and motion of cells in relation to cell membranes.

Data available substantiate the assumption that the nuclear membrane is permeable to large macromolecules, although technical difficulties favour a cautious interpretation. A critical survey of these findings has been given by Anderson (177).

Electron-microscopic pictures of the nuclear membrane of an amoeba have shown a pore structure with a diameter from 800 to 1200 Å, with a continuous layer on the outside and one layer with a porous structure on the inside [Bairati & Lehmann (178), Harris and James (179)].

#### NEURONS

Quantitative x-ray microradiographic studies have shown that various types of nerve cell differ with respect both to mass and to lipid content [Brattgård & Hydén (41)]. The mass values of retinal ganglion cells of rabbits were found never to reach those of control cells if the animals were born and lived in complete darkness for ten weeks. This applied even with subsequent adequate light stimulation for several weeks. The postnatal development of ganglion cells with respect to dry substance was also studied [Brattgård (78)]. A study on motor nerve cells from chick embryos with x-ray microradiography illustrated the effect of virus infection on the mass of these cells [Sourander (180)]. A striking drop took place in the mass of the nerve cell cytoplasm concomitantly with the increase in the virus titer; these changes were correlated with changes in the ultraviolet absorption. Using a new method for the determination of RNA in single neurons, Edström (181, 182) found lower values per nerve cell than those earlier reported in studies with ultraviolet microspectrography.

Bryant & Tobias (183) could confirm that the amount of light scattered by the crab nerve varies as a function of activity. Activity in the nerve was accompanied by a considerable decrease in scattering; in a stretched nerve on the other hand, activity was accompanied by an increase. The effect of ultraviolet irradiation on nerve function has been studied, and the conclusion was reached that radiation interferes with some photochemical process in the nerve [Boyarsky (184)]. X-ray diagrams have shown a similarity between fibrin fibrils and glia fibrils, and ultraviolet analyses have been used to corroborate these findings [Wilke & Kircher (185, 186)].

Studies on the submicroscopic structure of the myelin sheath have con-

firmed earlier observations that the structure involves alternate layers of lipid and protein material, but new findings have also been reported. Finean (187) concluded from x-ray diffraction patterns that, in the lipid layer, the longest lipid molecules are tilted or curled so that they do not contribute their extended length to the thickness of the leaflet. The effects of temperature on the x-ray diffraction patterns of nerves were found to be maximal between 0°C. and -2°C. and between 58°C. and 61°C. The results indicate the presence in myelin of a lipid or lipoprotein complex which seems to change irreversibly with temperature [Elkes & Finean (188)]. The effects of various solvents on the x-ray patterns of fresh and dried nerves were also studied; it was inferred from the results that myelin contains a highly-ordered lipid-lipoprotein complex [Elkes & Finean (189)].

New data have been provided by investigations with the electron microscope. In an extensive study on fresh nerves, Fernández-Morán (190) made observations which led him to state that there is a common pattern of organization in myelinated fibres of all sizes and in the so-called unmyelinated nerve fibres. He found the myelin sheath to contain lamellar membranes with an average thickness of 80 Å and a fine, granular structure. The axon was seen to contain filaments of indefinite length and a diameter of 100 to 200 Å. A new type of submicroscopic fibres was found with a diameter between 0.1 to 1  $\mu$ ; they consisted of a thin sheath formed by a tubular membrane 60 to 80 Å thick and exhibiting a fine, granular structure. Utmost caution in the investigation and interpretation of these delicate structures has been emphasized [de Robertis (191), Fernández-Morán (192)]. Cultured nervous tissue from chick embryos has also been subjected to such investigations [de Robertis & Sotelo (193)]. Sjöstrand (194) found the lamellae of the myelin sheath to be about 25 Å thick and the space between two such lamellae to be bisected by intercalated lamellae. Evidence has been presented that increased esterase and lipase activity in the proximal part of the nerve can be attributed to the regenerating neurites [Lumsden (195)].

#### SPERM AND EGG CELLS

Wilkins & Randall (196) took x-ray diffraction photographs of both isotropic and anisotropic sperm heads. The results suggest that the sperm heads of both types are composed of crystalline bundles of longchain nucleoprotein molecules, parallel to each other in the anisotropic sperm heads. It is interesting to collate these data with the results of studies of light scattering in DNA and with the suggested structure of the nucleic acid molecule [Rowen (197), Pauling & Corey (198), Watson & Crick (199)].

Bernstein & Mazia (200), investigated the properties of undissociated desoxynucleoprotein obtained from the sea urchin sperm by water extraction. Substance was found to have an elongated molecular form, 4300 Å long and 250 to 300 Å wide. The nature of the bond between the nucleic acid and protein was discussed, *Arbacia* spermatozoa were found to turn over or syn-



thetize RNA, and the experiments using  $P^{32}$  indicated that the midpiece may be the centre of RNA activity [Di Stefano & Mazia (201)]. Other investigations have been made on the microstructure, genesis, and properties of sperm cells [Hansson *et al.* (202), Watson (203), Friedlaender & Fraser (204)].

Various agents causing the egg to divide were found to liquefy the cortex [Wilson & Heilbrunn (205)]. Rugh (206) determined the radiosensitivity of the gametes of *Spisula*. The rate of incorporation of  $P^{32}$  into follicle cells of secondary oocytes of the rabbit proved to be higher than that of the primary oocyte [Aminoff *et al.* (207)]. The pigment granules in eggs of *Paracentrotus* were found to have a characteristic ultraviolet absorption spectrum indicating a chromoprotein [Monroy & De Nicola (208)]. In the blastula stage the granules would also contain nucleic acid. It has been shown that the cytoplasm of egg cells of the frog and sea urchin contain DNA and that the amount of DNA in the unfertilized sea urchin egg is considerably in excess of that which can be accounted for in the nuclei [Hoff-Jørgensen & Zeuthen (50), Zeuthen (209), Elson & Chargaff (210)]. It is certainly to be expected that the function of follicle cells will be the subject of future investigations.

Hultin *et al.* (211) studied different factors acting on sperm and egg surface at the fertilization of the sea urchin egg. A factor promoting the membrane elevation was demonstrated in the jelly coat; it was found to be released upon treatment with the extracts from egg or sperm.

#### ERYTHROCYTES

The use of ultraviolet microspectrography in haematological problems has been discussed by Thorell (212). Bragg & Perutz (213) made diffraction measurements of haemoglobin molecules. A direct determination of the electron density in one particular direction in the molecule has been made by Bragg & Perutz (214, 215) and Bragg *et al.* (216). Electron microscope studies of the fresh erythrocytes have shown that normal cells have an even surface, whereas agglutinated erythrocytes have a rugged, uneven surface [Block & Powell (217)]. Bernhard (218) demonstrated by means of the same method that erythrocytes have a dense inner structure with some degree of orientation. Moskowitz & Calvin (219) isolated several chemical compounds from red cell ghosts.

#### PLANT CELLS

The chloroplasts of plant cells and other photosynthesizing organisms have been the subject of several investigations. An extensive discussion of the development of chloroplasts is given by Straus (220). The chloroplast was found to have a membrane composed of an outer part, presumably containing lipids, and an inner layer of proteins. The grana inside the chloroplast are reported to have a lamellar structure with oriented lamellae 70 to 300 Å thick, reflecting a composition of protein and lipid discs [Thomas *et al.* (221), Thomas (222), Steinmann (223), Palade & Wolken (224)]. In a study



on *Beta saccharifera*, Leyon (225) could not confirm that the chloroplast has an inner membrane of grana. Evidence was brought forward to show that the grana consist of stacks of lamellae with the long axes arranged about normal to those of the chloroplast. The occurrence of cytoplasmic fibrils in the stroma of spinach chloroplasts is described by Thomas *et al.* (221). The structure resembled chains of tiny globules, chromidia, linked together by interchromidia. Bustraen, Goedheer & Thomas (226) measured the electron-scattering power of these structures and found the constitution of the chromidia to differ from that of the interchromidia. Thomas, Blaauw & Duysens (227, 228) studied the relation between the size of fragments of spinach grana and photochemical activity. Particles of a critical volume presumably contain 40 to 120 chlorophyll molecules. Below this size the inactivation of the particles proceeded gradually, indicating the occurrence of a rate-limiting enzyme in a quantity small compared to that of the chlorophyll. Evidence has been presented that the location of the red absorption band of chlorophyll-adsorbent complexes is dependent on the nature of the adsorbent, and that *in vivo* the chlorophyll may be adsorbed in the molecular associated state [Rodrigo (229)].

In the plant cell membrane, the cellulose is produced in the form of fibrils 100 to 200 Å thick in the primary wall; they become aligned in parallel in the secondary cell wall. Lignin and other substances are deposited between the fibrils [Mühlethaler (230 to 233)]. Birefringent measurements and x-ray diffraction photographs have been used to study the physical properties of the cell wall in conifer tracheides and wood fibres [Wardrop & Preston (234)]. The outer layer of each tracheide was found to be composed of cellulose chains lying in a flat spiral at an angle of 50° to the cell length, and at an angle of about 20° in the thicker central layer, the spiral being much steeper at this site. This high angular dispersion in the outer layer is responsible for the characteristic optical property of the wall. Microspectrographic and x-ray microradiographic data showed that the concentration of the carboxyl groups in the cellulose cell wall is greatest in the outer part of the fibre. The cellulose, on the other hand, was found to have its greatest concentration at the lumen [Asunmaa & Lange (235, 236)]. Frey-Wyssling (237) postulated that the cellulose elementary fibrils have a crystalline inner part which is covered by a paracrystalline peripheral layer. The spiral growth and spiral structure of plant cell walls have been investigated by x-ray diffraction and electron microscopy [Middlebrook & Preston (238, 239)]. Pictures of spirals in the protoplasm of cells of the growth zone have been obtained and a theory put forward for the spiral growth. In growing cells, the cytoplasm penetrates the cell wall, and at no stage in the development of a cell is there a clear-cut distinction between wall and cytoplasm [Preston & Kuyper (240)]. Preston's results indicate that the bulk of the cytoplasm in plant cells is not directly associated with cellulose synthesis, which seems to be confined to certain parts of the cytoplasm associated with a development of microfibrils. These

have a granular appearance, each granule being about 500 Å in diameter. The chemical composition and structure of the yeast wall are described by Northcote & Horn (241). Bawden & Kleczkowski (242) observed that visible light can inhibit the lethal effect of ultraviolet irradiation of plants. It has been shown that characteristics of the oxidant other than those associated with its standard potential affect the reducing activity of illuminated chloroplasts [Macdowall (243)].

#### EXTRACELLULAR STRUCTURES

*Connective tissue.*—Bear (244) published an excellent review of the structure of collagen fibrils, partly on the basis of their own results obtained with the x-ray diffraction technique, and discussed the problems critically. Randall *et al.* (245) summarized their results of studies on collagen from various sources and during development. They objected to the polypeptide chain-configuration in collagen suggested by Pauling, Corey & Branson (246) because of the infrared dichroisms observed [see also Fraser (247)]. They considered a possible explanation of the 640 Å period to be structures in the form of hydrogen-bonded sheets folded where a high concentration of polar side-chains occur. Such a structure would also satisfactorily account for swelling properties.

Small-angle x-ray diffraction intensities and Patterson distribution were obtained from tendon collagen [Kaesberg and Shurman (248)]. The Patterson distributions were interpreted in terms of the intraperiod fine structure observable in electron micrographs. The authors found evidence of the presence of a single high density band in wet, unstained collagen and a detailed band structure in wet, stained collagen. Further studies have been made on reprecipitated collagen. Bahr (249) filtered a rat tendon collagen solution through a filter with decreasing pore diameter, and obtained at a pore size of 5 μ premature precipitation of collagen having the regular period around 635 Å. Collagen formation in the rabbit skin was studied by Hakness & Neuberger (250). They used glycine labelled with C<sup>14</sup> to investigate the precursor to collagen. The results indicated that a soluble protein prepared from the skin is the precursor to a part of the skin collagen. Additional data have been provided on the submicroscopic structure of collagen from various sources [Hofmann *et al.* (251), Martin (252)].

Bairati *et al.* (253) did not observe any essential difference between the submicroscopic structure of particular tissue fibrils and that of collagen fibrils. Little & Cramer (254) found the reticulin from connective tissue to consist of thin lamellae of fibrils embedded in a supporting membrane 50 to 150 Å thick and presumably a glucoprotein. Day & Eaves (255) showed that the basic substance consists of membranes composed of fine fibrils and embedded in a structureless substance and that hyaluronic acid does not appear to be involved in the composition of these structures.

New data have been contributed to the discussion on the α-helix configura-

tion of polypeptide chains from proteins of the  $\alpha$ -keratin types and synthetic polypeptides [Elliott *et al.* (256), Fraser & Price (257), Crick & Cochran (258), Crick (259), Pauling *et al.* (260), Astbury & Haggith (261)]. The difficulties involved in the surmised simple structure of the  $\alpha$ -keratin protein have been stressed. The suggestion of seven-strand protein cables in parallel orientation offered by Pauling & Corey (262) does, however, fulfil the criteria, and a repeating unit of seven amino acid residues is believed to give rise to a seven-strand  $\alpha$ -cable about 30 Å in diameter. The x-ray patterns of hair, horn, and other  $\alpha$ -keratin proteins can be accounted for by such a unit.

The polysaccharide of nucleus pulposus has been isolated and identified [Malmgren and Sylvén (263)]. The chemical results and infrared spectra showed that the bulk of the nucleus pulposus polysaccharide is chondroitin sulphate or sulphate isomers. Orr, Harris & Sylvén (264) studied chondroitin-sulphuric acid from cartilage and hyaluronic acid from various sources with infrared spectroscopy, this being a sensitive method for detecting sulphur, which was found to be absent in sodium hyaluronate of human origin. Polarization microscopy on elastic cartilage showed that, if the tissue was tanned with sumach, the optical sign for the masked collagen fibrils was reversed but not that for the birefringent elastin fibrils [Schmidt (265)]. The phenomenon provides a differential diagnosis for these structures. Hirsch *et al.* (266) attempted to make a quantitative definition of changes with increasing age in cartilage by studying the polysaccharide-protein structure. They found a significant change in the ratio between these substances with increasing age and a coarsening of the submicroscopic fibrils. Shulman, Ferry & Tinoco (267, 268) studied the conversion of fibrinogen to fibrin. The results indicated that elongated fibrinogen polymers are dissociating in shorter particles when the protein concentration is reduced. Birefringence data implied that part of the fibrinogen is present in the form of elongated polymers.

*Bone tissue.*—A series of investigations using x-ray diffraction, x-ray microradiography, and autoradiography deal with the organization of bone tissue [Amprino & Engström (269), Amprino (270, 271), Engström *et al.* (272), Zetterström (273), Engfeldt *et al.* (274), Engström & Engfeldt (275)]. Low-angle x-ray diffraction measurements of bone have indicated that the hydroxyl-apatite crystallites are elongated, with their long axes parallel to the collagen fibres; they have a diameter of 60 to 80 Å and their length is about three times their width [Engström & Finean (276)]. The distribution of minerals was found not to be uniform, since osteons having a high content of organic and inorganic constituents alternated with osteons with a lower content. The Ca content of the primary periosteal bone proved to be higher than that of the secondary bone, and the calcification of new bone took place more rapidly close to the vascular channels. New osteons had a lower salt content than older ones. The same type of x-ray pattern was found in various types of bone tissue. The amount of inorganic salts incorporated into the bone depended largely upon the osteomucoid. The renewal of phosphate was

discussed in relation to changes in the bone collagen structure. The incorporation of  $P^{32}$  was found to be most rapid in the young Haversian systems. In calcified tendons, a more pronounced orientation of the mineral salts than in bone was noted. It is interesting to compare these results with those on the turnover of bone carbonate obtained by Buchanan & Nakao (277). They observed that a fraction of the carbonate in the bone of grown animals exchanged rapidly with a soluble carbonate system, but the greater part exchanged slowly. The turnover pattern was found to be similar in different bones in the rat. Martin (278) found collagen fibrils in bone to exhibit the same submicroscopic picture as those from tendon. The submicroscopic structure of dental enamel during development and in the adult stage is described by Wyckoff *et al.* (279, 280, 281).

*Muscle tissue.*—Horwath (282) found that the isotropic and anisotropic bands have a ratio of 1:1, independent of the state of contraction; he inferred that both types of bands contain contractile material. Mommaerts (283) gave a summary of the properties of actin and actomyosin. Ströbel (284) found that the contraction of a positive birefringent envelope around an isotropic or weakly anisotropic nucleus may be explained by the assumption of a coiling of the protein chains. Hansson (285) observed that the I-bands disappeared in the early stage of contraction before the usual band of contraction occurred. Pfeiffer (286) demonstrated by means of polarization microscopy, that the I-zone probably contains nucleotides. The double refraction of actin and myosin under normal and pathological conditions was investigated by Aloisi *et al.* (287). The submicroscopic structure of the myofibrils and their development were the object of study by Perry & Horne (288) and by van Breemen (289).

Morales *et al.* (290) obtained infrared absorption spectra of myosin, actin, and actomyosin; the spectra were found to be similar. Morales & Botts (291) studied the effect of ATP and other ions upon the configuration of the myosin particle.

Infrared spectroscopy of muscle protoplasm showed the occurrence in certain cells of a band at  $9.7 \mu$  which is absent in others despite physiological similarity [Wood & Sutherland (292)]. The spectrum of the muscle cell seems to be closely duplicated by that of the myosin. The so-called Lotmar-Picken (LP) diagrams have been studied by Bear & Cannan (293) and Huxley and Kendrew (294). They found that water extraction of muscles caused a disappearance of the LP-pattern,<sup>1</sup> and concluded that the substance giving the LP-diagram cannot be a protein. Bamford & Hanby (295) were able to confirm a fibre repeat of 5.3 to 5.4 Å. Pauling & Corey (296) found their muscle samples to contain 10 per cent of a crystalline material and about 90 per cent of protein with the  $\alpha$ -keratin structure. They also found that the crystalline substance which produces the LP-pattern gives the same diagram as poly- $\gamma$ -methyl-L-glutamate and therefore seems to be a polypeptide of large molecular weight.

Several new data on physicochemical changes in muscle compounds have been reported. The effect of various metal compounds and of crystalline digitalin (Digitoxin) on the physical state and contraction of actomyosin and the polymerization of globular into fibrillar actin have been studied. The mechanism of the inhibition of polymerization by Mersalyl (Salyrgan) is discussed, as well as the release of energy at the contraction of the actomyosin gel [Kuschinsky & Turba (297), Kuschinsky *et al.* (298), Turba and Kuschinsky (299), Kuschinsky *et al.* (300)].

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## GROWTH<sup>1,2</sup>

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### INTRODUCTION

The present review is restricted to the field of human growth and is further limited, because of space requirements, to those aspects of human growth and development which have been given the most attention in the last few years.

In view of the increasing interest shown in defects, developmental in origin and stemming from "insults" early in the developmental sequence, recent advances in this field are included. Further, since one specific abnormality, retrolental fibroplasia (RLF), is a postnatal defect, information about this unusual abnormality may now be summarized.

On the other hand, a good deal of what is published on human growth refers specifically to generalizations about the human growth process and the use of such information for the assessment or evaluation of individual growth. This, too, will be reviewed here.

Although considerable information has now been collected on the growth-inhibiting potentialities of specific hormones, differences in the growth-stimulating potentialities of anterior pituitary hormones, and the effect of specific ketonic steroids on osseous maturation, these subjects will not be included in the present review, belonging as they do to endocrinology.

### CAUSES OF GROWTH ABNORMALITIES OPERATIVE DURING INTRAUTERINE LIFE

As reviewed in an editorial in the *Journal of the American Medical Association* (1) many factors may modify the genetically-determined potentiality for normal growth and development inherent in the fertilized ovum. Leaving out the age of the ovum (overly mature ova may be somewhat more likely to be productive of abnormal embryos) and the "quality" of the fertilizing spermatozoon, these factors total seven. They are defective implantation, deficiencies in the maternal diet, infections, intoxications, endocrine disturbances, trauma, and penetrating radiations. To this list should be added fetal anoxia, shown to be important by animal experiments, notably those of Ingalls *et al.* (2) and Atland (3). Oxygen deprivation, or decreased ability of injured tissues to take up oxygen, may underlie many of the factors mentioned. To the extent that maternal age is a relevant factor, placental defects restricting the oxygenation of the fetal bloodstream may be actually responsible. At the present time parity (birth order) can not be discounted,

<sup>1</sup> The survey of literature pertaining to this review was concluded December, 1952.

<sup>2</sup> The following abbreviations are used in this chapter: ACTH (adrenocorticotropin); RLF (retrolental fibroplasia).

nor can it be separated from maternal age *per se*. Exactly what the contribution of the male gamete is to nongenetic developmental defects can not now be solved, although Dahlberg (4) suggests that overripe ova are more likely to be fertilized by Y-bearing sperm.

The increasing accumulation of knowledge, both experimental and clinical, on the nature of influences productive of intrauterine growth abnormalities no longer makes it tenable to suggest a genetic explanation for any and all developmental defects. Ingalls (5, 6, 7) has made out an excellent case for a multifactorial explanation for Mongolism, stating that, "While the causative agents of Mongolism are relatively numerous, the causative mechanisms are few in number and operate at about the eighth week of fetal life." It may be interesting to note that Worcester *et al.* (8) found that, while maternal age is of importance in Mongolism, when such offspring are statistically removed from a series of developmentally defective infants maternal age is no longer significantly related to the incidence of developmental defects.

Dietary deficiencies, experimentally induced during pregnancy, do result in a wide range of developmental defects in the offspring of laboratory animals. Warkany, in particular, has shown this to be true, noting aniridia, hydrocephaly, spina bifida, cleft palate, neurological, ocular, and skeletal defects occurring in the litters of vitamin-deficient mothers. Some proportion of developmental defects noted in human births must be attributable to vitamin deficiencies and maternal hypoproteinemia. However, except in longitudinal studies, for example Burke *et al.* (9), it is difficult to assemble satisfactory evidence. Women who will report the prenatal diet regularly and carefully are apt to be careful about what they eat. Women with dietary fads and fancies and no systematic appreciation of nutrition may over- or underestimate their actual food consumption, or actually fabricate dietary records.

As to the effects of penetrating radiations on the prenatal growth of the human infant (leaving out still meagre information from Japan) it is possible to say that radiation can be the cause of abnormalities of growth, but it is hardly possible to be more specific. Experimental (animal) data relating to this subject, as reviewed by Warkany (10), Russell (11), Fraser & Fainstat (12), and others, show that irradiation in the period following nidation more often leads to embryonic death than to anatomical abnormalities; at a later stage of development the offspring of irradiated mothers show many malformations and few deaths. Irradiating pregnant rats close to term results in few fetal deaths and no malformations. As might be expected, specific defects produced are rather closely related to developmental status at the time of irradiation.

Two reviews, appearing in 1952, have dealt with the possible consequences of accidental irradiation of the maternal pelvis during early pregnancy. Rubin (13) reported a three-generation follow-up, with no evidence in the second of anatomical defects, and presumably no evidence of mutational

effects. Russell & Russell (14) have discussed the possibility of developmental defects more intensively, noting that the critical period is from the second to the ninth week of pregnancy. (Some authorities would extend this through the thirteenth.) They recommend that when therapeutic doses of x-rays are indicated in women of child-bearing age, irradiation should be accomplished in the first half of the menstrual cycle, before a ripe ovum has had a chance to become fertilized.

Although not suggested initially by animal experiments, a great deal of information has been provided by epidemiological studies on the possible role of viral agents in the etiology of developmental defects. Specifically, some (if not all) viruses are able to pass the placental barrier and to bring about arrests in development. Thus, if the mother becomes infected during the first trimester, arrested fetal development may result in embryological defects, their nature and extent depending upon the time and duration of the infection. It is not known, however, to what extent this may be the direct result of viral penetration and to what extent it may be secondary to changes in the maternal physiology.

The influence of rubella in bringing about developmental defects has been so completely discussed ever since Gregg's studies of the Australian epidemic, that there is no need to review the subject further here, except to point out that defective offspring do not necessarily result from rubella in pregnancy, a belief that has caused complications in several Scandinavian countries where abortions may be performed legally if due cause is shown.

Recently, evidence has accumulated that a large number of viral infections, if experienced during early pregnancy, may lead to irregularities of embryonic growth. Grönwall & Selander (15) have indicated that developmental abnormalities may follow rubella, varicella, parotitis, hepatitis, poliomyelitis, and herpes zoster. While in some of these cases the *post hoc propter hoc* sequence may still be challenged, it is interesting to note the evidence now accumulating against the virus presumably responsible for infectious (epidemic) hepatitis. Kass (16) reports a case of hydrocephaly and microcephaly in the offspring of a mother who suffered infectious hepatitis during the second month of pregnancy. Wesp & Kellogg (17) described a case in which a composite monster was born to a mother who experienced hepatitis during the first trimester. And Bellin & Bailit (18) observed a case of portal cirrhosis in an infant whose mother was infected late in term. Sontag (see 19) has discussed the possible relationships between viral infections during pregnancy and organic brain damage observed in later life.

It should be realized, of course, that a great many substances, including sex hormones, may pass the placental barrier; antibiotics may be mentioned as well. In the modern world, with improved communication facilities and vastly improved standards of medical care, there are many more chances of a given conception coming to full term. Yet, at the same time, there is a somewhat increased chance for growth arrests during embryonic life. Considering the widespread use of hormones to minimize the chances of abortion



(20) and antibiotics to reduce the spread of infections, there may be a concomitant increase in the number of defective offspring, even neglecting the role of viral agents.

#### RETROLENTAL FIBROPLASIA: A DEVELOPMENTAL DEFECT ARISING IN EARLY EXTRAUTERINE LIFE

One of the most unique developmental abnormalities in man, retrolental fibroplasia, was not recognized as an entity until described by Terry in 1942. Specifically, retrolental fibroplasia, as described by Terry (21, 22, 23), Owens & Owens (24), Kinsey & Zacharias (25), Reese (26), and Gilger (27), includes both early vascular changes in the eye and the later changes with the characteristic retrolental membrane, retinal detachments, and gross changes leading to impaired vision or total blindness.

The ocular defects, which are invariably bilateral, are not only restricted to prematurely born or developmentally immature infants, but almost never develop in those with a birth weight exceeding 2000 gm. (27). The incidence of retrolental fibroplasia rises with the degree of immaturity at birth and is most likely to develop in infants beginning life with a birth weight under 1500 gm. (24). In the ten years that retrolental fibroplasia has been recognized, it has become a serious problem, not only to the clinician and the research worker, but also to school authorities. Cities such as Dayton, Ohio have had to establish special programs for children with vision impaired as a result of retrolental fibroplasia. An uncounted additional number of the prematurely born may exhibit lesser losses of visual acuity, or refractive errors, as a result of lenticular or retinal changes.

Unlike studies of many defects of developmental origin, such as those following maternal rubella, epidemiological studies have not contributed extensively to an understanding of retrolental fibroplasia. Even allowing for the failure to diagnose the ocular changes in the years prior to 1942, the increasing incidence of this defect, the rather large differences in the frequency of occurrence noted from region to region, and especially the apparent localization of retrolental fibroplasia to hospitals in the Northern section of the United States have been most puzzling, as observed by King (28). The increase in reported cases of retrolental fibroplasia has been out of proportion to the slightly improved chances for survival of the very premature infant (25). However, epidemiological studies showed, from the outset, that these ocular changes were not associated with a hereditary predisposition, nor were they part of a combination of congenitally acquired and progressive defects (28). As discussed by Paul (29), Silverman & Day (30), and Krause (31), the condition under consideration is developmental in nature, postnatal in origin, and restricted to infants developmentally most immature at birth.

The search for factors responsible for this condition took two directions, one being further investigation of early ocular development, and the second a hunt for unique factors in the management of the premature infant, which would account for the common occurrence of retrolental changes in one hospital and its near absence in another.



Taking a cue from Warkany's (32) experimental production of ocular defects in the offspring of vitamin-deficient rats and the evidence that some of the changes were not unlike those exhibited in retrolental fibroplasia, considerable attention was paid to dietary supplements (including vitamins A and D) used in premature nurseries. Kinsey & Zacharias (25) cautiously suggested a plan in 1949 whereby vitamins A and B and iron preparations would be withheld during the first two prenatal months. In a later report (1951) Kinsey & Chisholm (33) concluded that vitamin A is not the responsible factor in retrolental fibroplasia. Dancis, Lewis & Guy (34), after an experimental study at the Bellevue Hospital, also concluded that early use of vitamin A therapy is not responsible for this defect. In view of the vascular changes during the early stages of retrolental fibroplasia, and the known effects of vitamin E, it is not surprising that Owens & Owens (35) and Kaye & Rudolph (36), among others, suggested the use of vitamin E. However, the work of Reese & Blodi (37) and Laupus & Bousquet (38) does not support the hypothesis that hypovitaminosis E is either primarily responsible or that its use ameliorates the development of retrolental changes.

In addition to vitamins A, B, D, and E, attention has been paid to other aspects of the diet of the premature infant. Since retrolental fibroplasia was apparently rare in European hospitals using human milk preparations, there was a possibility that a return to this food might be beneficial. However, there is at present no evidence, according to Hepner & Krause (39), that human milk in itself contains any uniquely protective elements, or that bovine substitutes are involved.

Closely allied to the composition of the diet is the question of the electrolyte content and, by extension, the whole question of fluid retention, hypertension, possible ocular damage, and retrolental changes. Notably a high-electrolyte, high-salt diet should be fluid retaining, but it is doubtful whether it in itself is the responsible factor (39). Furthermore, the fluid-retention, hypertension hypothesis no longer seems to be tenable, according to Laupus *et al.* (40). Along this line may be mentioned the animal experiments of Hepner (41, 42), who attempted to produce retrolental fibroplasia in kittens by massive transfusions.

The use of adrenocorticotrophic hormone, in various stages of purification, or cortisone, was based on several assumptions, including the one that the adrenal response of the immature is insufficient, and that ACTH<sup>2</sup> therapy would be a means of correcting the presumed electrolyte imbalance. While Brown & Corner (43) and Bembridge *et al.* (44) reported favorably on the use of ACTH in "checking" the progress of retrolental fibroplasia in small series of subjects, many deaths reported by American workers and the lack of positive results do not favor either the hypothesis involved or the use of ACTH or cortisone in the management of this developmental defect. Reese *et al.* (45) reported 6 deaths out of 36 cases so treated, and no change in the course of RLF.<sup>2</sup> La Motte, Tyner & Scheie (46) obtained no evident improvement from ACTH or cortisone. Lanman, Guy & Dancis (47) obtained comparable negative results.

Among the other possible factors considered and rejected in explaining the etiology of RLF have been blood group incompatibilities (29), exposure to light (28), and a possible hyaluronidase inhibitor (48). While King (28) had earlier suggested light as a possible factor and recommended maintaining the prematurely born infant in a dark room, Locke & Reese (49), by experimental unilateral ocular protection of 22 premature infants, showed that light exposure was not a major factor.

The most profitable line of research on the etiology of this developmental defect has been the study of the oxygen concentration maintained in the incubator. Crosse & Evans (50) have pointed out that the increase in retrolental fibroplasia has been associated in time with the increased use of oxygen and "efficient" oxygen cots in the maintenance of the prematurely newborn. Previously LeLong, Renard & Rossier (51) pointed out the still fetal eye conditions prevailing in the prematurely born infants and the hazards of continuous oxygen therapy. Campbell (52) employed a careful experimental design and showed that 23 out of 123 prematurely born infants on high oxygen (40 to 60 per cent) developed retrolental fibroplasia in contrast to 4 out of 58 on low oxygen. Patz *et al.* (53) also showed a lower incidence of the disorder (13 per cent) among 37 infants on low oxygen, while 50 per cent of 28 on high oxygen developed signs of this disorder. At present, therefore, the evidence points to high oxygen concentration as the responsible factor, as previously reviewed by Szewczyk (54).

In considering retrolental fibroplasia, it should be remembered that this is a true developmental defect, though extrauterine in origin. The greater the degree of prematurity, the greater the hazard. But it is also true that the less mature the infant at birth, the longer the waiting time before the manifestations of RLF are completed.

Ordinarily when developmental defects are mentioned, maternal deficiencies or placenta-passing toxins are brought to mind. But retrolental fibroplasia is a defect, clearly developmental in nature, brought about by an environmental insult in extrauterine life through the use of measures intended to support life. Under these circumstances it may well be that other defects, not noted at birth, but assumed to be congenital or even inheritable, may actually be attributable to artificially-induced disturbances in the growth of still incompletely developed organs. With greater use of hormonal therapy, vitamin therapy, antibiotics, and bacteriostatic agents, especially on the least developed newborn, the possibility of bringing about unwanted developmental defects should be borne in mind.

#### TECHNIQUES FOR THE DESCRIPTION AND EVALUATION OF HUMAN GROWTH

*Involving time and some measure of size.*—In contrast to other forms of life whose modal patterns of increase have been subjected to comparatively sophisticated mathematical analyses, the treatment of human growth data has in general been simple. Of the various possible treatments of the data

reviewed by Medewar (55), one form is used in over 90 per cent of presentations. Greater decrees of sophistication, involving log-linear plots, log-log plots, the double log adaptation of the Gompertz equation used by Curtis (56), and other attempts to straighten the line plotted by mean values, have been few, and usually based on data collected by others. Much more energy has gone into the use of numerical data in attempts to appraise or evaluate the growth and development of populations and individuals. Most such attempts have been based on height-weight data alone, as described by Krogman (57). Thus the emphasis has been placed on the assessment of human growth, rather than on its mathematical description, a situation prevailing up to the present time.

Using a conventional age-size plot, with time as the horizontal coordinate and length (recumbent or standing) on the vertical, the age-size or "growth" curve of any human group investigated to date is characterized by the familiar rapid rise and later falling off to a slope of zero. Superficially, this curve resembles the curves of population growth, a similarity much commented on by Pearl, Robertson, and others. However, it is legitimate to enquire whether a curve representing the population size of a yeast colony is inherently the same as the growth curve of a multicellular organism. Moreover, the human growth process, an exaggeration of the primate growth curve rather than being simply autocatalytic, includes a number of discrete phases mediated by one or more growth stimulating hormones, and segmental growth itself is limited by epiphyseal union. The fact is that individual growth curves differ significantly from the averaged curves employed for illustrative purposes, and such individual growth curves involve points of inflection not paralleled by the curves of population growth. Hence both the inclusion of the human growth curve as an example of a "typical" growth curve and the validity of an averaged growth curve both may be challenged. For discussions of these points, see Davenport (58), Zuckerman (59), Brody (60), Tanner (61), Medewar (55), Kinsell *et al.* (62), and the review by Garn (63).

Apart from these considerations, in using any table of normative values or a graphic chart based on such values, there is the question of the applicability of the norms and the degree of conformity to be expected on the part of an otherwise healthy child. Krogman (57) and, to some extent, Watson & Lowrey (64) have discussed the first point. No studies have been published which satisfactorily answer the second. The Fels Composite Sheet, described by Sontag & Reynolds (65) and Watson & Lowrey (64), is unique in that it can be used with any desired norms since all findings are converted into standard scores or T scores. Here, as with more conventional charts, the clinical significance of any degree of departure from an established line is not automatically evident, a problem further discussed by Tanner (61).

Inasmuch as height and weight are recorded separately on conventional growth charts, there is the perennial problem of relating the two measures. Unfortunately it is the common assumption that the same percentile position in both height and weight is an indication of "normal" build. Since weight

increases more rapidly than height, this is not true except at or near the 50 per cent percentile. In a recent study by Greulich (66) Guamanian children were reported to be at a lower percentile position in weight than in height in comparison with American children. Gavan (67), however, objected to the inference drawn by Greulich, pointing out that the weight increases as the cube of height. Replotting the data, Gavan demonstrated that both American and Guamanian children fell along the same trend line. The difficulty exhibited here may be minimized in part by recording the standard score of both height and weight (as is done in the Fels Composite Sheet). However, since the distribution of weight is hyponormal there are certain drawbacks to this system as well.

Most of the studies reported in the last few years, however, have employed the usual presentation, and newly devised growth charts, such as that by Meredith (68), have been of the conventional form. For details, see Vickers & Stuart (69), Stuart & Meredith (70, 71). Height and weight data have been published on many groups previously unreported, and height-weight data have been made available for a number of groups previously unmeasured. In all, measurements on nearly 1,000,000 children have been summarized in the last few years. References to these studies will be found in the *Child Development Abstracts*, the *Yearbook of Physical Anthropology*, and in the *Quarterly Cumulative Index of Medical Literature*. As examples one may cite Meredith's data on Oregon schoolboys (72), Boulanger's report on French children (73), the study by Peguignot *et al.* (74) on rural and urban French children (167,000 in all), Majumdar's data on 140 boys from an obscure tribe in India (75), and considerable data on the birth size and weight of Israeli (76) and American (77) babies. While such studies add to the body of data and may provide information transiently useful in the assessment of individual growth, it can not be claimed that they constitute main advances in the understanding of growth in man. In contrast, reporting annual increments, forming so-called velocity curves as Tanner terms them, may be of greater value both theoretical and actual. One such study by the Merediths (78) should be noted.

The more theoretical aspects of human growth have not been entirely neglected, and the utility of conventional methods of appraisal has been questioned. Tanner (61, 79), who had previously shown the fallacies inherent in the per-surface area and per kg. body weight ratio standards, has completed detailed analyses of the reporting of growth data and the assessment of growth and development in children. Besides considering such problems as curve fitting and touching on the Wetzels, DeToni, and Correnti auxograms, he has also considered the longitudinal and mixed longitudinal and cross-sectional methods of growth appraisal. Careful attention to these two papers will not only aid in the design of research programs but should also assist those responsible for longitudinal growth studies in obtaining maximum results from their research design.

Finally, the paper of Zuckerman (59) should be mentioned. Though the

entire symposium of which it represents a part is not at hand, it is evident that the work so magnificently begun by Brody, Thompson, Medewar, Count, and others is being extended further with derivative benefits to the whole field of human growth.

*Involving the relationship between two measures of size.*—In contrast to methods of describing or appraising human growth which plot some variable such as the size of a given organ as a linear, exponential, or logarithmic function in relation to time, a number of methods have been suggested by Huxley and others which relate two measures to each other. This makes it possible to show, in graphic form, not only the increase in size of an organism, but also the ratio between the two measures. Since in neither child nor adult are height and weight linearly related, a satisfactory description may be attained by plotting height against the cube root of weight (or weight against height cubed) as discussed by Gavan (67). The log-log plot has been used most extensively by Wetzel (80). These plots make use of approximations that satisfactorily fit various groups of data. They need not represent fundamental laws of growth. In similar fashion the technique of plotting "height-age" against "weight-age" attains linearity, but by a contrived method. All such methods are most useful in assessing growth in relation to the previously conceived trend line, and here a linear plot is of assistance. On the other hand, simple linearity is not something to be attained at all costs in purely descriptive studies. As Richards & Kavanaugh (81) pointed out, curve fitting should have as its ultimate purpose the addition to biological knowledge. What is the gain if, in straightening a curve, some important property of growth is lost in the process?

Perhaps the most widely considered method of growth appraisal suggested in the last two decades is the "grid" method of Wetzel (82, 83, 84). Essentially, the grid is a log-log plot, with a trend line indicating normative data, a series of parallel lines representing constant log height log weight ratios, cross lines representing size equivalents, and a more conventional system of evaluation involving both size and time. The grid involves certain assumptions about the constancy of the log height/log weight relationship ("physique" as Wetzel terms it). Notably, the grid makes provision for children differing in the height-to-weight ratio (other systems of growth assessment do not, or do so clumsily), and it includes an alignment chart for the estimation of caloric requirements. This latter feature may well be eliminated since there is now experimental evidence that the composition of the body, rather than mass or surface alone, determines the caloric needs, as shown by Miller & Blyth (85). The grid principle, however, has been adapted for infants by Wetzel (86) and for other populations by Koch (87) in England, and Mühsam & Zaslany (88) in Israel. Variants have been constructed for Japanese, and some similarities may be noted in De Toni's (89) auxological method, and other systems now in extensive use in Italy.

The grid has been used in a number of studies relating to normal growth, dietary deficiencies, dietary supplements, congenital disorders, or simply in-

adequate growth. Wilde (90) plotted height-weight data of Aleut children from the Pribilof Islands on the grid, and concluded that, since the majority fell in the upper (A) channels, they were in good physical condition. Garn & Moorrees (91) compared the channel positions of Aleut children from Nikol'ski Island with Wilde's data, and observed that the grid channel distributions were closely comparable, despite differences in nutritive status and general health. Among others, Cohen & Abraham (92) used the grid technique on allergic children, and Litman & Bosma (93) investigated growth failure associated with poliomyelitis using this analytic device. More recently Richards (94) used the grid in place of the more conventional methods of appraisal in the study of children with congenital heart disease, and Coleman (95) used this method in appraising the course of celiac disease. Wetzel, himself, active in the use of the grid, has shown a possible association between loss of channel position and family dislocations and has used changes in the grid position as evidence for the growth-promoting value of vitamin B<sub>12</sub> (96). Wilde (97), in a second publication, has employed another feature of the grid, the so-called developmental levels, to demonstrate the growth-promoting value of a dietary supplement. Spies & Dreizen (98) have used the grid method to illustrate the effect of milk supplements.

For so widely used a device, actual analysis of the grid and experimental tests of its assumptions have been relatively few. Apparently in most cases the grid has either been accepted or summarily rejected without detailed investigation. As subsequently reported, there have been some comparisons of the grid with other methods, as discussed by Mann *et al.* (99) and reviewed by Krogman (57) and Tanner (61). Certain aspects of the grid have been challenged by Simmons & Greulich (100) and Bruch (101). Among the strictures raised was the use of "developmental levels" as a measure of maturation, independent of and apart from such measures as skeletal age (osseous stage), overt signs of maturation (breast and pubic hair development), and menarche. Since size and maturational status are correlated, the grid may be a partial substitute for such other measures. But since the correlation is not high, height and weight alone, however combined, fail to provide the requisite information *in toto*.

Certain aspects of the grid have been questioned by Scandinavian investigators, Andersen (102) and Dössing (103). Both observed that the grid plots of individual children were not necessarily straight line, and even the smoothed lines, mathematically straightened, did not in general parallel the channels printed on the grid form. Dössing, using height-weight data on 5082 boys and girls, further demonstrated systematic age-changes in channel distribution. In like vein Garn (104), using both short-term and long-term longitudinal data, observed a tendency for girls to move down-channel during late pre-puberty and up-channel during the steroid-mediated phase of physical development. This tendency was also noted when normative height-weight data from six different groups (including Navajos and Japanese) were plotted on the grid. For other criticisms, note Kallner (105).

While these findings do not invalidate the use of the grid either as a research tool or as an adjunct to appraisal, they indicate that the grid, like any attempt to fit individual growth data to massed data curves, must be employed with certain reservations. Doubtless a theoretical homozygous population on a standardized diet would show fewer deviations; and, with suitable corrections for the different growth patterns of the male and the female respectively, actual and predicted growth patterns would more nearly coincide. The trouble is that such populations do not exist in man. And individual differences in the pattern of maturation and the time and sequence of epiphysial union will continue to make the log-log plot as much of a Procrustean bed as the more conventional plots involving age and measures of length, circumference, or weight. However, recognizing the fact that any graphic representation of growth data is only a curve of fit, the grid represents a much more imaginative approach to the appraisal of human growth than most workers in the field of human growth have attempted.



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# RADIATION EFFECTS ON MAMMALIAN SYSTEMS<sup>1,2</sup>

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This review will be concerned with the acute effects of high energy radiations on mammalian systems. Its purpose is twofold; to delineate many of the recent papers in this area<sup>1</sup> and to place the more important contributions in some perspective to the over-all physiology of radiation injury. Complete coverage of radiation effects is not intended, owing to the vast literature and the consequent necessity of excluding many papers to conform to the allotted space.<sup>3</sup> Several surveys of the more general aspects of radiation effects on living systems have been presented recently (1 to 7); cellular (8, 9), embryological (10), and carcinogenic (11) actions of irradiation have also been covered. The extensive report of acute radiation injury in man resulting from accidental nuclear reactions should be consulted (12). These cases represent radiation injury not complicated by the effects of heat and blast.

It is appropriate to say a word about trends in mammalian radiobiology by way of introduction. We may note an increasing interest in the more immediate physical and chemical changes in irradiated tissue. Such endeavors have been greatly influenced by present concepts of the modes of energy transfer and the recognition that certain, apparently primary, events may be modified experimentally. Greatest attention continues to be focused, however, on the disordered physiology as manifested by effects on growing and developing systems generally and by pancytopenia, bleeding, inanition, infection, altered immune reactions, and carcinogenesis, specifically. In this area, there is a growing awareness that injury and recovery may be influenced to a considerable extent by the physiological interplay in the organism as a whole.

## THE RADIATIONS

While all of the ionizing radiations produce more or less similar biological effects, their efficiency can vary considerably. This depends apparently upon the energy absorption in space and time and also upon its distribution within the organism. For most effects, excluding those that are related presumably to very small volumes, biological effectiveness increases with increase in linear ion density or, more appropriately, in linear energy transfer. Gray (13) has emphasized that the rapid variation of efficiency with ion

<sup>1</sup> The survey of literature pertaining to this review covers the period from January, 1951 to June, 1953.

<sup>2</sup> The following abbreviations are used in this chapter: DNA (deoxyribonucleic acid); RNA (ribonucleic acid).

<sup>3</sup> This refers in particular to miscellaneous effects on skin, bone, gonads, and nervous system.

density occurs between about 100 ions/ $\mu$  and 1000 ions/ $\mu$ , corresponding to the region between 200 kev x-rays and 2 Mev neutrons. Other things being equal, differences in efficiency between 200 kev x-rays and harder radiations should be comparatively small.

Woodard & Spiers (14) have determined that the depression of phosphatase activity in bone is about 1.4 times greater with 100 or 185 kev x-rays than with 1000 kev radiation. The relative reduction in enzyme activity is of the same magnitude as the energy absorption ratios derived from suitable models. Ting and associates (15) find that 200 kev x-rays are about 1.5 times as effective as 23.5 Mev x-rays from the betatron for production of leucopenia in mice. This difference is due mainly to an effect on granulocytes, perhaps as a consequence of differences in energy dissipation in the bone marrow cavities, although other interpretations are possible. Betatron radiation is 20 to 40 per cent less effective than 150 to 400 kev x-rays for acute lethality in rats (16), greying of hair in mice (17), and regression of tumors in mice (18). Gamma-rays are also about 40 per cent less efficient for acute killing than conventional x-rays (19). Greater effectiveness ratios, based on mean survival time of mice after supralethal irradiation, have been reported (20); it is not clear, however, whether the dose rates for  $\gamma$ - and x-rays were comparable. It is curious, moreover, that mice were killed by total-body doses as small as 100 r. Differences in biological efficiency are not always apparent in this region of ionization density (21, 22) and, in fact, fast electrons may be more effective in certain instances (23).

Tobias *et al.* (24) have determined that high energy deuterons and protons have about the same efficiency for lethal action in mice as 200 kev x-rays. The ionization density is nearly the same for these radiations. Blood and tissue changes after irradiation with 190 Mev deuterons are proportional to roentgen equivalent doses and similar to changes induced by other ionizing radiations (25). Typical acute radiation effects have also been noted in mice after injection of tritium oxide (26).

Hollcroft & Lorenz (27) have observed that the integral dose of 186 kev x-rays necessary to cause 50 per cent death in mice is only 1.4 times that of  $\alpha$ -particles from injected radon. This unexpectedly low value may possibly be attributed to the lack of homogeneity in distribution of  $\alpha$ -particles among the various tissues. We may recall that the lethal effects of various radioisotopes may be additive or synergistic depending upon their distribution (28, 29). The importance of dose distribution is indicated in other recent work (14, 30). Notwithstanding the possible contribution of the uneven distribution of radiation after radon injection, there is independent evidence that biological effectiveness for lethal action in mice reaches a maximum with increase of linear energy transfer and then declines (31). The complexities of interpretation, in contrast to the situation in small biological objects such as bacteria, is illustrated further by comparison of the efficiency of x-rays and injected radon on regression of a transplanted lymphosarcoma (32). The dosage required to induce tumor regression is comparable for a subcutaneous

implant but greater for x-rays in case of an intramuscular implant. Moreover, there is a definite systemic effect on tumor regression after total body x-irradiation (32).

The rate of irradiation complements ionization density in the interpretation of radiation actions. Differences in efficiency between continuous  $\gamma$ -irradiation and fractional x-irradiation can be explained in terms of these parameters (19). The time-intensity dependence for cutaneous effects in man is greater with high speed electrons than with conventional x-rays, perhaps because of a greater recovery factor with the former (33). Thomson & Tourtellotte (34) note that the  $LD_{50}$  for mice exposed to  $Co^{60}$   $\gamma$ -rays is relatively independent of dose rate above 4 r/min. Variations in  $LD_{50}$  between dose rates of 0.7 and 42 r/min. can be accounted for by a single recovery constant with a half time of 25 hr. The situation becomes more complex at very low dose rates. A striking dose rate dependence for x-rays occurs in young birds (35) and, to a lesser extent, in newborn rats (36). Exposure of 2- to 3-day old chicks to 1000 r at 15 r/min. results in 75 per cent mortality within 24 hr.; there is little early killing with dose rates of 6 r/min. unless older chicks are used (35). Early killing is associated with renal failure (37). It appears from dose fractionation studies that the over-all time of exposure is more important than dose rate in eliciting these effects (38). The significance of the over-all time of exposure to x-rays is indicated in other experiments with month old mice in which total dose fractionation and periodicity of treatment were varied (39).

The insidious nature of radiation effects is discussed by a number of authors, particularly from the point of view of genetic hazards. Several pertinent papers may be listed in passing (40 to 43). Permissible levels of exposure must obviously depend on the quality of radiation in so far as biological effects depend on ionization density. Extrapolation of the acute effects of whole-body irradiation from animals to man is discussed by McLean *et al.* (44).

#### DEVELOPMENT OF INJURY

*Biochemical effects.*—Metabolic derangements induced by high energy radiation may result from a primary attack on enzyme systems and other biochemical mechanisms, or as a consequence of cellular breakdown and the various physiological ramifications. Although a number of biochemical effects have been described from time to time, their relationship to the development of injury is incompletely understood. Since comparatively little energy induces profound change, attention has been directed to possible effects on enzymes and other key substances that might provide the necessary amplification for the biological end result.

Considerable interest has been focused on sulfhydryl-obligate enzymes, which are generally considered to be intimately associated with cell metabolism, growth, and reproduction. This is due, in large measure, to the facts that sulfhydryl enzymes are quite radio-sensitive *in vitro* and that certain

reactions catalyzed by sulfhydryl enzymes may be inhibited *in vivo* (45). Subsequent observations of a protective effect of sulfhydryl-containing substances against radiation injury of cells, plants, and animals (7) heightened interest in the sulfhydryl hypothesis of radiation action. This interesting concept is challenged by more recent observations.

It is noteworthy that x-irradiation has no immediate effect on sulfhydryl levels in a number of tissues (7). This is consistent with theoretical considerations; the available sulfhydryl in tissue exceeds by several orders of magnitude the amount that could be oxidized directly by lethal dosages of radiation even in the absence of naturally occurring protective substances. More delayed changes in sulfhydryl concentration have been observed in irradiated tissue, but these appear to be a consequence rather than a cause of injury (46 to 49). Similar effects have been reported for a variety of conditions and are apparently nonspecific (46). Shacter *et al.* (46, 50) have observed a decrease in plasma sulfhydryl levels in irradiated rats that coincides with a delayed rise in plasma polysaccharide; these changes are considered to be related to regenerative processes.

Although sulfhydryl enzymes may be inhibited by ionizing radiations under certain conditions, there is ample evidence that -SH enzyme inactivation is neither a selective nor a uniform process *in vivo* (51 to 55). It should be noted that some of the cellular effects of sulfhydryl reagents and of x-rays are similar (56, 57); however, the same situation may obtain for other chemicals. Sulfhydryl poisons in general do not reproduce the radiation syndrome. Injection of sodium malate prior to irradiation does not alter mortality appreciably (58); moreover, radiation toxicity is not affected when *p*-chloromercuribenzoate, a sulfhydryl complexing agent, is administered to mice either before or after whole body x-irradiation (59). Postirradiation cysteine can reverse the effect of a toxic dose of mercuribenzoate given prior to exposure, but radiation toxicity is unaltered under these conditions. There is independent evidence suggesting that cysteine protection against radiation effects in mammals is related to hypoxia rather than to a selective effect on sulfhydryl enzymes (60, 61); this point will be discussed later.

Other enzyme effects have been described. Alkaline phosphatase activity of bone is decreased following local irradiation with x-rays (62) or radium (63). Phosphatase activity of other tissues may be unchanged or increased after whole-body irradiation. There is little change in the activities of several nonmercapto enzymes of liver in irradiated rats, although liver catalase is decreased in mice 24 hr. after exposure. These findings have been reviewed (64). An increase in activity of several tissue cathepsins is reported by Feinstein (65). The effect, which is related to the absolute amount of radiation rather than to the lethal or morbid response, is considered to be a consequence of destruction of an enzyme inhibitor present in certain blood cells. Dubois *et al.* (52) find that x-irradiation decreases citrate accumulation in a number of radiosensitive tissues of fluoroacetate treated rats. Citrate accumulates in the livers of similarly treated male rats in contrast to the lack

of effect of fluoroacetate in nonirradiated males. This may be attributed to an effect of irradiation on the testes (66).

In general, the respiratory rate of tissues obtained from irradiated animals or of tissues irradiated *in vitro* is either unchanged or decreased. An exception is the brief increase in respiration of rabbit marrow homogenates prepared immediately after x-irradiation of the intact animal (67). More delayed changes in tissue respiration and glycolysis are attributed to diminished or altered cellularity (53, 54). As shown by Ashwell & Hickman (54), absolute quantities of several respiratory enzymes in spleen are reduced in proportion to splenic involution. Whole-body irradiation does not impair the capacity of mouse brain to utilize oxygen or to metabolize exogenous phosphorus (68). A decrease in oxidative phosphorylation has been observed in the spleen (69); the reason for this is not obvious.

Recent observations indicate that oxygen consumption of the animal as a whole is not altered materially by irradiation (70, 71, 72). A small decrease in exhaled carbon dioxide occurs in mice immediately after exposure to 2000 r; this presumably results from depression of glucose catabolism (73). The absence of any profound changes in metabolic rate of the intact animal in the presence of possible alteration in endogenous respiration of radiosensitive tissues is not unreasonable, since tissues that account for most of the oxygen consumption are notably radioresistant.

There is general agreement that irradiation affects nucleoprotein metabolism; the significance of such derangements is not clearly understood. Depolymerization of thymus DNA<sup>2</sup> *in vivo* is related to radiation dosage (74). It is diminished in animals injected with thiourea or breathing 10 per cent oxygen during irradiation, which suggests that it is probably initiated by activated water reactions. Continuous irradiation of tongue epithelium with P<sup>32</sup> decreases the stainability of nuclei with the Feulgen reagent after prior treatment with deoxyribonuclease (75). Tissue cultures of the Walker rat carcinoma show a diminished ultraviolet absorption 48 hours after irradiation with dosages of the order of 50,000 r; earlier changes are not apparent (76). It is not known whether decreased absorption is due to some change in the physical state of nucleoproteins or to loss of nucleoproteins from dying cells. Blood levels of total nucleotide, adenylic acid, adenosine diphosphate and adenosine triphosphate are unaltered in irradiated mice (77). A progressive increase in urinary deoxyribonuclease activity has been detected in irradiated rats (78).

Nucleic acid concentration and turnover, as measured by isotope uptake are decreased in a number of tissues (53, 79 to 86). Abrams (79) notes that synthesis of both DNA and RNA<sup>2</sup> is depressed in marrow and intestine. Payne *et al.* (80) find that P<sup>32</sup> incorporation into cytoplasmic RNA of liver is increased, while DNA and nuclear RNA turnover are decreased. According to Holmes & Mee (81), there is an early inhibition of DNA turnover as measured by P<sup>32</sup> uptake, but there is little effect on RNA, in the Jensen rat sarcoma. Thomson *et al.* (82) have observed that the DNA concentration



per nucleus in irradiated marrow is unchanged and that the decrease in RNA occurs mainly in the cytoplasm. Although there is some indication of a decreased capacity of certain tissues to esterify phosphorus, it is unlikely that this defect is entirely responsible for the derangements in DNA metabolism (53, 54). Recovery of DNA turnover in x-irradiated mice is somewhat enhanced by repeated injections of embryo mash or extract; survival is only slightly improved by this procedure (87).

Protein synthesis is not decreased, even though nucleic acid turnover is depressed (79, 81). Incorporation of  $C^{14}$  into tissue protein may actually be increased soon after irradiation (83, 88). An early transient increase in the synthesis of hemin and of globin by spleen and marrow has also been reported (89).

Glucose catabolism may be decreased immediately after exposure of mice to 2000 r (73). Liver glycogen accumulates in fasted animals after single lethal irradiation (90, 91). The effect is apparently independent of the adrenals (48). Liver glycogen is greatly depleted after massive irradiation until death (92) or after fractional irradiation with 400 r on each of five consecutive days (93). Glycogen depletion after fractional exposure can be partially prevented by treatment with lactoflavin or pyridoxine. Sublethal irradiation may decrease hepatic glycogenesis in guinea pigs during the second postexposure week (94). These effects apparently reflect the altered physiological balance rather than direct liver injury.

Coniglio *et al.* (95) have been unable to detect disturbances in lipid balance in irradiated rats. Total lipids, phospholipid, cholesterol, and vitamin A concentrations of the livers of irradiated and pair-fed controls are similar. A decrease in lipid content of livers of fasted irradiated mice has been observed after massive exposure of the hepatic area (96). It is suggested that the appearance of a fatty liver after irradiation is related to decreased food intake. Hewitt *et al.* (97) have described early changes in serum lipoproteins of rabbits that are considered to be prognostic of subsequent death. Total lipoprotein is increased and low-density components are converted to higher density. Since heparin injection facilitates recovery of lipoprotein levels and toluidine blue is, in this instance, radiomimetic, it is considered possible that there is an early acute heparin deficiency followed by release of large amounts of heparin by the third day. Present evidence indicates that circulating anticoagulants are inconsistently present (98, 99, 100). Although lipoprotein values at 30 hr. after irradiation parallel the degree of killing (97), causality is not necessarily implied. It may be recalled that heparin injection potentiates radiation lethality (101).

Soberman *et al.* (102) report an increase in plasma volume and a decrease in red cell volume in irradiated dogs; total-body water, extracellular space, sodium space, and plasma electrolytes show little change. Kohn (103, 104) has detected a pattern of change in the principal constituents of guinea pig and rat plasma. He notes that discrepancies exist between the radiation syndrome and the alarm reaction. Bowers & Scott (105, 106) find that there



is an early loss in potassium from radiosensitive tissues of the rat, an exception being testes. There is a comparable loss from bone even when the marrow is excluded. Sodium is decreased along with potassium, although a subsequent sodium increase may be noted in some tissues. Tissue water may increase while sodium is declining. Atypical changes in spleen weight are reported. An anomalous increase in the albumin-globulin ratio of irradiated rat sera has been traced to the presence of an ether-extractable factor (107).

*Cellular effects.*—The reader is referred to the recent review of cellular radiobiology by Sparrow & Forro (9). Considerable attention continues to be focused on the antimitotic effects of irradiation. Friedenwald & Sigelman (108) have shown that the duration of mitotic inhibition after local x-irradiation of the corneal epithelium of the rat is proportional to dose and is apparently related to destruction of a critical substance formed at a steady exponential rate during interphase. The rate of recovery of mitosis is independent of the damage, suggesting that recovery occurs by replacement and not by repair. The duration of mitotic block is said to be comparable for dose rates of 6.5 and 430 r per min. and for voltages of 8 and 240 kev. It is increased by other conditions such as anesthesia and exophthalmus and decreased by pretreatment with 2,3-dimercaptopropanol (BAL). Although inhibition is similar in rats breathing 5 or 100 per cent oxygen during irradiation of the eye, the possibility of direct diffusion of oxygen into ocular fluids complicates interpretation.

Widner *et al.* (109) have utilized the effect of x-rays on cell division to determine the mitotic time of different tissues. Differences in mitotic indices are a consequence primarily of variations in intermitotic times. It is of interest that nitrogen mustards differ somewhat from x-rays in their effects on mitosis and are not suitable for this purpose. Brues & Rietz (110) have determined that the amount of  $\beta$ -radiation required to reduce liver mitosis by one-half is about 1 rep per hr. over a 48 hr. period. They consider the possibility that radiation death and the induction and regression of tumors as a result of irradiation may be related to genic changes in cells. The importance of mitotic and genic effects in the lethal process is considered in other work (110 to 112). Glücksmann (113) emphasizes the importance of radiation effects on differentiation as well as on mitosis and genetic reactions. Wilson *et al.* (113a) note that embryos are more susceptible to injury when cellular differentiation commences.

Mole (114) points out that the death of many types of cells after moderate irradiation may be unrelated to an effect on mitosis. The great sensitivity of the small lymph node lymphocyte (115) and of the thymocyte (116) may be recalled; these cells rarely divide and yet are as sensitive as mitotic cells. Schrek & Ott (117) have suggested that a common physiological process may be affected in the nucleus of the lymphocyte and in the mitotic nucleus in general. Radiosensitivity may be related to the ratio of nuclear and cytoplasmic nucleic acids (110, 118).

Whether the primary damage invariably occurs in nucleus or cytoplasm

is a moot question. Zirkle & Bloom (119) have developed a microbeam for localized irradiation of parts of cells as small as  $2.5 \mu$ . Irradiation of Newt heart chromosomes in tissue culture with a few dozen protons induces abnormalities, while massive dosages to the cytoplasm produce no immediate effect on chromosomes or on mitosis.

Extensive descriptions of the histological sequelae of irradiation of mice (120, 121), rats (122), hamsters (123), and swine (124) have been presented. The chronic effects of repeated low dose irradiation of mice have also been reported (125).

*Blood.*—Depression of the cellular elements of blood is a result mainly of the necrotizing and antimitotic action of radiation on hematopoietic tissues. However, blood loss and other ramifications of the altered physiological balance contribute to the peripheral blood picture. The usual pattern of change in peripheral blood has been seen in x-irradiated monkeys (126). Eosinopenia is not evident until the fourth day after 600 r and coincides with the onset of severe neutropenia; it apparently reflects the depression of blood formation generally rather than an adrenal-mediated response. Pyknotic lymphocytes appear in peripheral blood 3 hr. after irradiation of rats with 400 r (115). Karyorrhexis of granulocytes may be noted in guinea pigs after irradiation with only 10 to 25 r (127). Repeated low dose irradiation of dogs with 10 to 25 r weekly leads to an increase in immature granulocytes by the eighth week, which is paralleled by the situation in the marrow (128). Lymphocytes with bilobed nuclei seen in cyclotron workers have also been detected in dogs exposed to low indeterminate levels of cyclotron irradiation (129).

*Blood forming tissues.*—The sequence of events in marrow has been appraised by Rosenthal *et al.* (130), who observed that reticular cell transformation to blood cells is completely inhibited during the first week or so after median lethal irradiation of rats. Marked destruction of erythroid elements was noted while myeloid cells showed an accelerated maturation in addition to aberrant forms. Enhanced myeloid maturation may account for the transient granulocytosis sometimes seen during the first day after exposure. Rugh *et al.* (123) note that sensitivity of cell types in hamster marrow decreases from lymphocytic elements to myelopoietic to erythropoietic. The comparative radiosensitivity of erythroid and myeloid tissues, as reflected by regeneration of red and white cells after phlebotomy, has been investigated by Valentine and associates (131, 132, 133). Recovery from a standard anemia induced by bleeding prior to irradiation with 200 r is only slightly less rapid in irradiated than in control cats. It appears that erythropoietic tissue is less sensitive to radiation injury than myelopoietic, but this may be a consequence of the preferential influence of phlebotomy on the relative recovery rates of the two tissues (131, 132). Of particular significance is the finding that hematopoietic tissue of cats subjected to repeated whole-body x-radiation with 200 r over a period of 18 months shows no permanent functional impairment (133).

Trowell (115) has contributed a significant paper on the radiosensitivity of lymphocytes in which he emphasizes the nonspecific nature of the cytological damage produced by x-rays. The dose required to induce nuclear pyknosis in 50 per cent of lymph node lymphocytes 5 hr. after irradiation is 275 r in tissue culture and 150 r *in vivo*. This difference can be attributed, for the most part, to the relative anoxia in the center of the lymph node culture. These results compare favorably with recent observations on the *in vitro* sensitivity of small thymocytes, for which the LD<sub>50</sub> as determined by eosin-stained cell counts is about 125 r (116). Lymphocytes of blood and of duodenal villi are more resistant than those of the lymph node, a reflection perhaps of the role of aging, differentiation, and environment on radiosensitivity (115). While the killing of lymphocytes appears to be mainly a direct consequence of their radiosensitivity, remote effects on lymphoid tissue have been observed from time to time. Price (134) has shown that a distant effect can be demonstrated, particularly when the volume of irradiated tissue is small. The relative magnitude of direct and remote effects on lymphoid tissue depends, for the most part, on the integral dose.

*Anemia.*—It is generally conceded that radiation-induced anemia may be more severe than that anticipated solely from cessation of erythropoiesis. Hemorrhage and red cell destruction have been considered, therefore, as additional factors in its pathogenesis. The absence of a direct lytic effect of median lethal irradiation on erythrocytes *in vivo* has been shown rather conclusively by Kahn & Furth (135), who failed to detect a difference in the fate of Fe<sup>59</sup> labeled cells injected immediately before or after exposure. Thermal fragility of rat erythrocytes may be elevated somewhat during the first hours after total-body exposure to 600 r (136), but the effect is transient and its significance is not obvious. Large dosages are generally required to bring about hemolysis *in vitro* (137). It is pertinent in this connection to record the observation of Sheppard *et al.* (138, 139) that x-rays disturb a highly organized system that participates in selective potassium accumulation by the red blood cell. After irradiation *in vitro* with 5000 r and above, potassium is lost from erythrocytes and quantitatively replaced by sodium with little osmotic disturbance. This phenomenon does not depend apparently upon an effect of irradiation on glycolysis or on cholinesterase and, unlike many types of radiation action, is not influenced by elimination of oxygen during exposure.

Davis *et al.* (137) report an increase in urinary bilirubin when renal bile fistula dogs are irradiated with 150 to 250 r. They attribute this to cessation of red cell formation, destruction of hemoglobin-containing red cell precursors, and absorption of extravasated blood. Red cell destruction by toxic materials liberated from damaged tissues or from infectious organisms (140) may also be a factor. The importance of red cell leakage in the pathogenesis of anemia has been clearly shown by the work of Furth and co-workers (141, 142, 143). Large numbers of erythrocytes appear in the lymph within several days of irradiation, at which time extensive erythrophagocytosis

toxis and hemosiderosis may be noted in lymph sinuses. The elevation of serum and tissue iron observed in irradiated rats (144, 145) may be explained by these events along with the inhibition of erythropoiesis. The homeostatic increase in plasma volume during the second week after irradiation (146, 147, 148) contributes to the apparent anemia as manifest by cell counts.

*Abnormal bleeding.*—The cycle in the concept of the etiology of radiation hemorrhage is virtually complete; current investigators are inclined to agree with the earlier conclusion that thrombocytopenia is the major factor in the pathogenesis of abnormal bleeding. Prevailing evidence suggests that circulating anticoagulants are inconsistently present and play a relatively minor role (98, 99, 100). Some of the discordant observations in this area are apparently related to differences in experimental technique and to the complexities of their interpretation. Further work has shown that the clotting defect is generally well correlated with thrombocytopenia (98, 99, 149, 150). As shown by Jackson *et al.* (99), diminished prothrombin utilization after x-irradiation follows closely the decline of platelet levels. Ferguson *et al.* (151) indicate, however, that the defect of prothrombin consumption may not be due entirely to reduction in number or quality of blood platelets. They cite observations in dogs poisoned with Au<sup>198</sup> in which there was some variance in the temporal relationship between prothrombin consumption and platelet levels. Although the events after Au<sup>198</sup> injection and whole-body x-irradiation are not entirely comparable, a similar suggestion has been made by others on the basis of a few experiments with protracted  $\gamma$ -irradiation (100).

Prothrombin concentration is not altered (99, 149), nor is there a deficiency of the precursor of serum prothrombin conversion accelerator (152) or of the plasma antihemophilic factor in blood from x-irradiated dogs (153). Whole hemophilic blood with normal platelet levels accelerates the clotting of irradiated dog blood (153). This is not the case with platelet-poor hemophilic plasma. Platelet transfusions have been shown, moreover, by Dillard *et al.* (154, 155) to reverse the coagulation defect and to prevent bleeding in an irradiated dog. More data of this sort are obviously desirable. Multiple transfusions of whole blood are ineffectual (156). The more recent experiments in this area have been discussed by Cronkite *et al.* (155).

Notwithstanding the recent negative evidence concerning heparinemia as a contributing factor to radiation hemorrhage, it should be noted that changes have been seen in tissue mast cells, generally considered as a source of heparin. An increased number of mast cells has been reported to occur in the thymus of hamsters during its inversion stage after whole-body irradiation (157). The significance of the apparent increase has been questioned by Smith & Lewis (158), who employed whole tissue mounts of the hamster cheek pouch and mouse mesentery to visualize the changes in mast cells. They observed aberrations of the mast cells resulting in their complete disruption about one week after lethal whole-body x-irradiation. This process is considered to represent the mode of secretion of heparin-containing ma-

terial. Whether this phenomenon is in any way related to the hemorrhagic syndrome or to other effects of irradiation remains to be seen. Monkhouse *et al.* (100) have determined that irradiation does not affect the amount of heparin released during anaphylaxis unless a suboptimal amount of antigen is employed, in which case there is a small increase in blood heparin. They were unable to detect heparin in the blood of irradiated animals apart from anaphylaxis, even in the presence of frank hemorrhage. The fibrinolytic activity of serum and urine is reported to increase four to five days before death in dogs dying with extensive pulmonary hemorrhage after total irradiation with 450 to 800 r (159).

**Blood vessels.**—There is some evidence that alteration in vascular integrity plays a role in the hemorrhagic syndrome. Necrotic lesions and infection doubtless contribute to initiation of hemorrhage; whether there is a more primary effect of radiation on vascular permeability and fragility is largely undetermined. Haley and co-workers (160) have observed petechial hemorrhages in the capillary bed of the rat mesoappendix during the first day after exposure to 600 r. This takes place before significant depression of the blood platelets and is not accompanied by any impairment of blood flow. Smith, Svihla & Patt (161) have determined that massive dosages of irradiation, in excess of 10,000 r, are required to induce vascular damage in the bat's wing; even with these dosages, however, hemorrhage is not apparent. The most provocative evidence relating to capillary fragility as a major factor in the abnormal bleeding is derived from studies with flavonoids. Papers continue to support (162, 163, 164) and to dispute (165, 166, 167) the fact that rutin and related flavonoids are effective in minimizing radiation hemorrhage and mortality. The most complete evaluation has been made by Dauer & Coon (165), who concluded that rutin did not alter mortality of mice, rats, and guinea pigs when given parenterally or orally both before and after x-irradiation.

Reference has already been made to the flooding of lymph by erythrocytes (141, 142, 143). Wish and associates (168) find that labeled plasma and erythrocytes, Evans blue, and colloidal radiogold, in general, disappear faster from the circulation of x-rayed than from that of normal mice and rabbits. Maximum alteration occurs during the second post exposure week and may be correlated with the period of greatest bleeding. That augmented disappearance of various tagged substances is indicative of increased permeability is perhaps strengthened by the finding that macrophage function is not altered appreciably (168, 169). In view of the capillary obstruction and local impairment of blood flow seen in *in vivo* preparations (161), it is difficult to say whether these effects are a direct result of the action of radiation on the vascular endothelium. It should be pointed out that there is no evidence for increased permeability or fragility of renal glomeruli and, therefore, that such changes are probably not typical of irradiated capillary endothelium generally. Changes comparable to those of aging may be induced in the tunica media of elastic arteries of young mice by irradiation (170).

A vasodepressant material similar to ferritin has been detected in the blood of rats during the first week after x-irradiation; a vasoexcitor material appears during the second week (160). This sequence is the reverse of that reported for shock states. The significance of these findings is not readily apparent; on the whole, the evidence for generalized circulatory disturbance after median lethal irradiation is not impressive. That the early transient hypotension in irradiated rats is neural in origin is suggested by its absence in the spinal animal (171).

*Gastrointestinal effects.*—Many of the manifestations of irradiation of the whole body are identified with injury of the gastrointestinal tract. The contribution of intestinal injury to the over-all lethal effect depends upon species as well as dosage. Concerning the latter, Quastler *et al.* (172) note that the mean survival time in mice over the range of 1000 to 12,000 r is three to four days and that early killing occurs only if a large portion of the intestine is irradiated. Cohen & Cohen (173) have computed that the specific sensitivity of the abdomen of the rat is 1-1/2 times greater than the average sensitivity for the body as a whole. A transient and remarkably early increase in tonus and motility of the small intestine of rats has been observed by Conard (174) after x-ray doses of 100 r and above *in vitro* and *in vivo*. These effects are considered to be a consequence of direct action of radiation on cholinergic elements in the intestinal tract. They are apparently unrelated to the decrease in cholinesterase activity of the small intestine that occurs after the initial period of augmented contraction (175, 176). It may be noted here that various cholinergic blocking drugs have little effect on radiation lethality (177).

The weight of the stomach and of the small and large intestine of the rat is decreased during the first few days after irradiation (178). These effects are not a result of altered hydration, nor can they be attributed solely to decreased food intake. Early changes in weights of the contents along the gastrointestinal tract reflect the delayed gastric emptying (178, 179, 180). Goodman *et al.* (179), employing a quantitative dye procedure, observed a decrease in absorption availability of the small intestine after whole-body irradiation of rats. This could be attributed mainly to changes in gastric transit. It appears, however, that there is little, if any, basic impairment in absorption of fat (181) or protein (182) in irradiated mice during the first four days after exposure. Unhydrolyzed protein is not absorbed from the gastrointestinal tract of either the normal or irradiated mouse (182); it seems important to determine whether this situation would obtain several days later when bacteremia of enteric origin is manifest. Lipid absorption in irradiated and pair-fed control rats is comparable over a 28-day period (95). The observations of Jennings (183) are in substantial agreement, for he found that enteral administration of protein hydrolysates is as efficacious as parenteral administration in lowering the heightened sensitivity of irradiated protein-depleted rats. Forced feeding may be detrimental to the



irradiated normal rat; this has been amplified in recent experiments and related to the stasis occurring principally in the stomach (180).

Loss of body weight is observed in a number of species and is generally considered to be a reasonably good indicator of the severity of radiation injury. However, W. W. Smith *et al.* (180) present evidence that indicates that the weight pattern is mainly characteristic of the species rather than of radiation dosage or lethality. Guinea pigs may show no weight loss during the first week after an LD<sub>50</sub>; yet the body weight of rats is depressed markedly and that of mice is intermediate. The extent of weight loss after comparable lethal dosage is inversely related to the radiosensitivity of the three species; changing the weight pattern by enforced fasting does not alter the sensitivity, however. Notwithstanding the species variation, weight loss in the fed rat may be quantitated to the dose of radiation as shown independently by D. E. Smith *et al.* (184) and Nims & Sutton (185). The early weight changes are related mainly to anorexia. Identical weight patterns may be noted in fasted and fasted-irradiated rats (70, 185). This strongly suggests that x-irradiation does not alter greatly the over-all metabolism or degree of tissue hydration. Nevertheless, there is the suggestion of a negative nitrogen balance in rats during the first week after irradiation which can not be attributed to decreased food intake alone (186, 187). It is curious that the early excessive nitrogen excretion was greater with 600 r than with 1000 r (186). In other studies increased nitrogen excretion is related to the decreased food intake, although this is not the case for the increased urinary excretion of certain of the B vitamins (188). The results of recent experiments indicate that oxygen consumption is not altered significantly in irradiated rats (70), mice (71), and guinea pigs (72).

One might suppose *a priori* that deranged nutrition contributes to the total picture after whole-body irradiation. While a low dietary protein for some time prior to irradiation increases the susceptibility of rats, a similar diet for several weeks after exposure is relatively ineffectual (189). Pyridoxine restores the resistance to P<sup>32</sup> poisoning of mice deficient in the vitamin but does not alter the killing of normal animals (190). Addition of cobalt to the diet before and after exposure decreases mortality of x-irradiated mice (191). This is probably related to a specific effect on hematopoietic tissues. The beneficial effect of dietary cabbage in guinea pigs is believed to reside in its content of vitamin P-like substances which reduce capillary fragility (192). Addition of powdered liver to a basic ration (193), or of cottonseed oil (194) or of small amounts of methyl linoleate (195) to a basal fat-free diet is reported to lower the mortality rate of rats to fractionated but not to single lethal irradiation. Studies with obese mice reveal that the presence of normally utilizable fat does not affect survival time nor over-all lethality after acute irradiation (196). Whether a more subtle disturbance of metabolism and nutrition contributes significantly to the effects of median lethal irradiation remains to be seen.

*Immunity and infection.*—The effects of irradiation on immune reactions and on susceptibility to infection have been the subject of intensive investigation. The literature to 1950 has been reviewed by Taliaferro & Taliaferro (197). Miller and co-workers (198) have extended their earlier studies and conclude that septicemia caused by microorganisms of enteric origin is an important factor in death of mice exposed to median lethal dosages of x-rays. They find that a number of antibiotics are effective in reducing mortality in mice; of these, streptomycin is the most efficient (199). An inconsistent action of streptomycin on radiation lethality in mice is reported by others (200, 201). Mice treated with both streptomycin and somatotrophic hormone maintain their weight, but mortality is only slightly decreased even though streptomycin alone is effective in this instance (202). Bennett *et al.* (140) conclude from analysis of blood cultures that infection appears to be related to lethality in dogs surviving the first two weeks of irradiation. The normal bactericidal activity of rabbit serum is depressed a few days after whole-body x-irradiation (203). Furth *et al.* (204) find that aureomycin therapy minimizes bleeding and ulceration of the gastro-intestinal tract of irradiated dogs; there is no substantial effect on the peripheral blood picture or mortality. Treated animals show a lower incidence of positive blood cultures but a greater incidence of fecal organisms (205). A positive effect on mortality occurs when irradiated dogs are treated with terramycin; in this instance there is no delay in onset of clinical symptoms as noted with aureomycin (206). Bleeding appears to be the major cause of death in treated as well as in control groups. Aureomycin and terramycin have been shown to alleviate diarrhea in irradiated rats; body weight recovers more rapidly in treated animals, but ultimate mortality is not influenced appreciably (207). Gustafson & Koletsky (208) have observed that pretreatment of rats with terramycin for 48 hr. before x-irradiation is protective, possibly because of some alteration in the intestinal flora. There are other possible effects of the antibiotic, however.

The contribution of specific types of infection to the heterogeneity of antibiotic response is emphasized by Marston and associates (209). They point out that the presence of positive or negative cultures is not an indication necessarily of the contribution of infection to mortality. The cause of the bacteremia remains a moot question. As shown by Osborne *et al.* (210) bacteremia and intestinal damage are not always related, since the former may occur in mice irradiated with abdomen shielded. The oropharynx may be the portal of entry in this instance. For the present, bacteremia may be interpreted best in terms of the severe leucopenia and altered immunological reactions. Necrotic lesions in accessible areas are probably contributory. Bacteremia is relatively unimportant in early death following massive irradiation (201, 210).

A number of papers support the fact that irradiated animals are more susceptible to injected bacteria, viruses, and toxins and that irradiation and infection may be synergistic in regard to lethality (211 to 217). Shechmeister



and associates (216) have determined that sublethally irradiated mice show an increasing sensitivity to an airborne infection during the first 15 days after exposure. Kaplan *et al.* (217) find maximum sensitivity to a standard streptococcal infection between three and seven days after irradiation of C-57 black mice. Penicillin is effective in eliminating death resulting from the induced infection despite the profound leucopenia. Cortisone and x-rays are synergistic in the production of lethal infections (218).

The effect of x-rays on antibody formation has been subjected to quantitative appraisal. Kohn (219), employing antisheep hemolysins in the rat, observed changes in antibody formation when irradiation occurred either before or after antigen injection. Maximum inhibition was noted when irradiation preceded the antigen; however, a delay in peak hemolysin titer occurred even when the animals were injected two to four days before exposure. Dixon *et al.* (220) have determined that the precipitin response of rabbits to labeled bovine gamma globulin may be divided into radiosensitive and radioresistant phases; the former persists for about 12 hr. and is concerned with initiation of antibody formation. Irradiation does not alter the response to a second injection of antigen once antibody formation has begun. It is suggested that synthesis of antibody occurs in radioresistant tissues. A critical stage of injury to hemolysin formation in rabbits has also been described by Taliaferro *et al.* (221). Marked inhibition of the immune reaction occurs when antigen is injected from 12 hr. to 21 days after x-irradiation; there is little effect when animals are injected 6 hr. after exposure. In contrast to the results noted previously, the anamnestic response to a second injection of antigen was, in this instance, as sensitive to irradiation as the initial response. Antibody formed in animals irradiated before or after immunization has the same immunochemical characteristics as that formed by nonirradiated animals (222).

*Physiological balance.*—Since high energy radiations are dissipated at random in a heterogeneous and highly integrated system, many different effects may ensue, some of which are not a direct consequence of energy absorption. This situation differs only in degree from the cell to the tissue to the total organism. It is necessary, therefore, to contend with the physiological interplay in the system as a whole. It is well known that injury and recovery are dependent, to some extent, upon interactions between irradiated and nonirradiated areas. Damage to specific regions, e.g., a lymph node or a tumor, is also generally more severe after a total body exposure than after local irradiation. These effects may be attributed to the liberation of non-specific toxic materials from irradiated tissue, to hormonal influences, and to the sparing action of nonirradiated tissue.

While some evidence for circulating factors has been obtained, its significance is not fully appreciated. Ellinger (223) considers that histamine may be responsible for some of the biological effects of irradiation. Hiemsch (224) notes that cutaneous sensitivity to histamine is increased in guinea pigs after total irradiation; he concludes, however, that histamine accumulation

does not play a decisive role in the general injury leading to death. The protective effect of parabiosis has been confirmed (225, 226); it is significant that neither adrenalectomy (227, 228) nor splenectomy (228) of the nonirradiated partner alters the protection appreciably. Early cross-circulation (229) and blood transfusion (230) have also been shown to afford some protection in irradiated dogs, but this has not been confirmed (231).

Potential of local radiation effects by total exposure may be contrasted with the protection afforded against certain manifestations of the latter by shielding comparatively small volumes of tissue (232 to 241). It may be noted also that tissues from irradiated chick embryos survive longer when transplanted to nonirradiated hosts (242). The implications of these effects will be considered in the concluding section.

Several observations support the fact that irradiated animals are generally less able to cope with severe stress (243, 244, 245). Moderate degrees of stress may be well tolerated after minimally lethal irradiation (246, 247). Considerable attention continues to be placed on the role of the adrenals in the development of, and recovery from, radiation injuries. It is known from earlier work that ionizing radiations, in common with other noxious stimuli, induce changes that are presumed to reflect an increased demand for the adrenal cortical hormones. This functional response appears to be mediated by the pituitary. A number of papers support the concept of a nonspecific adrenal response (248 to 254). Differences between the alarm reaction and the radiation syndrome have been observed, however (103, 104, 255).

Confirmation of the synergistic lethal action of whole-body x-irradiation and adrenalectomy has been reported (234, 256). Daily injections of desoxycorticosterone acetate or of adrenal cortical extract enable the adrenalectomized rat to survive sublethal irradiation (256). It is significant that cortisone has been shown to augment a number of acute radiation sequelae in animals with intact adrenals (257, 258, 259). A beneficial effect of cortisone treatment has been reported after irradiation of the heads of mice (260). These findings are perplexing in view of the anomalous observation that there was little difference in lethality whether irradiation involved the whole body or was confined to the head. Betz (252) notes that ACTH treatment after irradiation increases mortality of rats; this agrees with earlier observations [reviewed in (64)]. The report of a therapeutic effect of ACTH (261) is not impressive because of the small number of animals used. Several nonspecific pretreatment procedures lead to a small improvement in survival (252). This is attributed to increased adrenal cortical resistance; other interpretations are possible, however. It may be noted that adaptation to severe exercise (243) or cold (245) does not modify lethality significantly.

Edelmann (262) has determined that adrenal shielding during irradiation increases the survival of rats. The reason for this is not entirely clear, particularly in view of the recent findings of Edwards & Sommers (227) and of Schneider *et al.* (228). The former were unable to detect any fundamental difference in radiation reactions as a consequence of adrenalectomy of

shielded or irradiated parabionts. The latter observed that the adrenals of irradiated rats were capable of sustaining nonirradiated adrenalectomized parabionts. Moreover, absence of the adrenals did not compromise protection of irradiated animals by parabiosis. These results strongly suggest that the adrenals of lethally irradiated rats suffer no basic impairment.

There is some evidence of altered thyroid function as judged by  $I^{131}$  uptake after lethal irradiation of rats (263). It is claimed that surviving animals have hyperactive thyroids, while the reverse is true of dying animals (264). Hyperactive thyroids are not seen in irradiated castrates (265). Leucopenia and anemia are reported to be somewhat more severe in thyropivic than in euthyroid rats (266), but this is controversial (267). Hypothyroidism is said to potentiate lethality of rats (266); however, other studies reveal that thyroidectomy does not alter survival time or mortality of irradiated animals (268). The latter agrees with earlier observations. Toxicity may be enhanced when desiccated thyroid is given after irradiation (269). The radiation-induced depression of the mitotic index of mouse epidermis is not altered by thyroid administration (270).

#### MODIFICATION OF INJURY

This subject has been reviewed recently by the author (7); hence the present discussion will be confined to the latest papers and to a summary of the efforts in this area. The modifying factors may be grouped into two categories according to their general mechanisms of action. One class is concerned apparently with the more immediate physiochemical ramifications of energy transfer, the other with the events responsible for injury to specific physiological systems or to recovery from such injury. Oxygen, sulfhydryl substances, and other pharmacological agents that are related to oxygen availability fall into the former classification. Tissue shielding and transplants, pretreatments with phenylhydrazine, foreign protein, estrogens, and other hormones are examples of rather specific procedures.

Storer & Hempelmann (271) have determined that the decreased lethality of the chilled newborn mouse is a consequence of hypoxia. The protective effect of extreme hypothermia during irradiation is diminished when the infant animals are allowed to breathe pure oxygen; it is not enhanced in the absence of oxygen. Devik (272) finds that hypoxia maintained during x-irradiation of mice with 200 r decreases the frequency of chromosome aberrations in hematopoietic cells. Since certain protective chemicals including cysteine (dosages are not stated) did not reduce chromosome injuries, it was concluded that the former act on the cytoplasm, while the action of hypoxia is confined mainly to chromosomes. This conclusion seems unlikely, since a protective effect of glutathione on radiation induced chromosome breakage has been seen in plant cells (273). There is independent evidence that suggests that cysteine may act, at least in part, by diminishing the availability of oxygen (60, 61, 116). Moreover, as shown by Patt *et al.* (274), differences in the magnitude of protection by cysteine against the effects of gamma and fast

neutron irradiation in mice are in essential agreement with the inverse relationship between ionization density and the extent of the oxygen effect.

Forsberg (275) notes that cysteine pretreatment minimizes the decrease in nucleic acid turnover in irradiated mice, and Hall (276) finds that tumor fragments are similarly protected. A cellular site of action is implicated in the latter studies; this is also apparent from work with irradiated thymocytes (116). Similar peripheral blood changes have been seen in cysteine-treated and control irradiated rats (277); the significance of this is not obvious, since leucocytes recovered more rapidly in control animals receiving 800 r than in those exposed to 400 r. Other observations reveal a uniform protective effect against the hematologic and other acute sequelae such as spleen involution and lethality (7). The findings are generally suggestive of a true dose reduction by cysteine in the sense that primary mechanisms are involved (274, 278). For the present these protective effects may be interpreted best in terms of some interaction with, or interference in the production of, one or another of the reactive products of irradiated water.

Bacq, Herve and associates (279, 280, 281) have summarized their work with cysteinamine ( $\beta$ -mercaptoethylamine); in the interests of space only a few of the original papers will be referred to here. This substance is more effective than cysteine on an equimolar basis when given intraperitoneally to mice. It is somewhat more toxic, however (282). Cysteinamine affords a general protective action against x-ray effects; it has been shown to reduce the radiosensitivity of reticulocytes *in vitro*, ciliates, pea roots, mice, and rats (279, 281). In this respect, it is similar to cysteine; yet, unlike cysteine (7), it is reported that cysteinamine does not decrease the radiosensitivity of tumor cells and, in fact, may be useful in the treatment of chronic leukemia (281). Cysteinamine has been used clinically to counteract the nausea and vomiting of radiation sickness with an apparent salutary effect (283); in this regard it resembles a number of unrelated substances. It is difficult at present to interpret the apparent diversity of action of this chemical.

Maisin *et al.* (284) have observed that cysteamine is effective in rats when given after irradiation if the liver has been shielded by lead. This interesting observation has not been substantiated (282). Bacq *et al.* (281) consider that the protective action of mercaptoethylamine in animals may be related to protection of a regeneration factor rather than to prevention of injury. The evidence upon which this is based is hardly conclusive in view of the difficulty of quantitating many radiation responses with dose in the lethal range (7). Recent observations indicate that the sparing of comparatively few critical cell types may exert a profound effect on recovery.

In view of the negative action of cystine (7), it is interesting to note that cystinamine also enhances the survival of mice when it is administered before x-irradiation. This may be attributed to its reduction to cysteinamine *in vivo* or to the formation of histamine; both phenomena are reported to occur (279, 281). Cystinamine, unlike its reduced counterpart, does not protect pea roots. Large doses of histamine and other amines have been shown to

protect mice (279), possibly because of the decreased tissue oxygen tension resulting from vasomotor reactions. Epinephrine, enteramine (Serotonin), and beta-hypophamine (Pitressin) are also protective to mice when administered prior to irradiation (285, 286).

It has been suggested that the protective action of sodium nitrite and ethyl alcohol in mice may be related to accelerated decomposition of hydrogen peroxide formed in irradiated water (287, 288). In this connection it is worth noting that large doses of azide or hydroxylamine, which are known to poison the catalase system, also reduce mortality of mice when given before x-irradiation (289). Small amounts of these substances do not increase the radiosensitivity of tumors in rats.

We may turn finally to the modification of injury and recovery of rather specific physiological systems. Reference has already been made to the protection afforded against the effects of total-body x-irradiation by shielding small volumes of tissue. The role of the shielded spleen has been investigated most extensively, especially by Jacobson and his collaborators. These studies have been reviewed recently by Jacobson (290). The most striking protective effects of spleen shielding on mortality and recovery of hematopoietic tissues have been seen in mice; effects in other species are less impressive. Whether this can be attributed to differences in the spleens or in the relative contribution of different mechanisms to lethal effects among the various species can not be stated with certainty; however, the former seems more likely. Even the mouse presents revealing age and strain differences. Spleen shielding is relatively ineffectual in the puberal mouse (290); there is a relatively small effect in adult C-57 black mice as compared with adult strain A mice (217, 291). Kaplan & Paull (291) have inferred from this that the protective effect of spleen shielding may be genetically conditioned and related to the importance of the spleen in the hematopoietic system of each strain.

Spleen transplants and homogenates are also highly effective in promoting hematopoietic recovery and enhancing survival when given during the first day or two after irradiation (290, 292, 293). Biological factors such as age, strain, and species are also operative here (293, 294, 295). Homogenates of spleen from week-old mice exhibit greater activity than do those from adult mice; moreover, as noted previously for spleen shielding, there is little effect when puberal mice are the recipients of spleen homogenates. Spleen homogenates afford relatively little protection to rats (294).

Recent experiments by Cole *et al.* (296) in which mouse spleen homogenates were subjected to differential centrifugation in sucrose media reveal that the protective factor is associated with the cell nuclei fraction. Their evidence suggests that the active factor is noncellular. Cole & Ellis (297) have also determined by enzymatic analysis of spleen homogenates that the protective activity resides largely in a desoxyribonucleoprotein. This represents a significant contribution to interpretation of shielding phenomena; however, it is by no means certain that a mechanism of this sort is operative in each instance of protection by shielding or tissue transplants.

Storer *et al.* (298) find that lead shielding of small amounts of ectopic marrow induced in the tail of young rats by previous abdominal implantation decreases x-ray lethality. Shielding of normal tails containing fatty marrow is ineffectual. It appears from these experiments that the protective effect of marrow shielding does not depend on a more rapid rate of recovery of irradiated hematopoietic tissue. It is suggested that the shielded tissue tides the animal over the critical period of injury. Lorenz and co-workers (299, 300) have extended their observations on the modification of injury by bone marrow injections. Histopathologic analysis of irradiated animals treated with bone marrow indicates that initial destruction of hematopoietic tissue is unaltered, but that regeneration is enhanced (300). The magnitude of the effect is somewhat dependent on the route of administration. Positive effects with heterologous marrow are inconsistent. Enhanced regeneration of lymphoid tissues occurs in animals irradiated with the thigh shielded, or injected with homologous marrow after total exposure (301). Regeneration is not influenced by injection of thymic cells. Various leucocyte-stimulating factors do not modify radiation lethality appreciably (302 to 305). Rats in which polycythemia has been induced by repeated exposure to high altitude show only a relative anemia after x-irradiation; however, lethality is somewhat potentiated by the procedure (306).

The evidence as a whole indicates that the modifying influence of spleen or bone marrow shielding, spleen homogenates, and bone marrow suspensions is related rather specifically to damage of the hematopoietic system and its sequelae. The precise mechanism of protection must be regarded as unsettled. There is no evidence that these factors influence the disturbances in other physiological systems.

It is appropriate to conclude this survey by noting that moderate x-irradiation of young or adult animals has no obvious effect on the capacity to learn (307).

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## PHYSIOLOGICAL ASPECTS OF GENETICS<sup>1,2</sup>

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### GENE DUPLICATION

A considerable amount of evidence indicates that deoxyribonucleic acid is capable of duplicating itself, a property also possessed by genes. (By a self-duplicating material, we mean one which plays some essential role in its own production.) Watson & Crick (1) have proposed a new structure for deoxyribonucleic acid which not only takes into account the existing analytical and x-ray diffraction data but also seems capable of explaining the mechanism of duplication. Their model consists of two helical chains coiled around the same axis, the purine and pyrimidine bases on the inside, the phosphate groups on the outside. The chains are held together by hydrogen bonds between the bases, the adenine residues of either chain being bonded specifically to thymine in the other, and similarly guanine to cytosine. The sequence of bases along one chain is not restricted, but once fixed the sequence along the other chain is determined. This complementarity, which is the most novel feature of the structure, suggests that duplication takes place by separation of the two chains, followed by the synthesis of its complement alongside each chain. The model is supported by recent x-ray diffraction studies (2, 3).

### VIRUS GENETICS

*Bacteriophage.*—The papers presented at a symposium on Bacteriophage, held at Royaumont, France, in the summer of 1952 have been published (4).

The following composite picture of the life cycle of bacteriophage emerges from recent studies on coliphage T2 by Hershey & Chase (5) and Visconti & Delbrück (6). The infective particle, tadpole-like in shape, consists of a protein coat or membrane surrounding a core which contains DNA.<sup>3</sup> The particle attaches to the bacterial cell by the end of its tail. Hershey & Chase have established by isotopic labelling experiments that the DNA passes into the bacterium, whereas the protein membrane remains outside and apparently does not participate in subsequent events. This separation of protein and nucleic acid components probably accounts for the observation of Doermann (7) that infective phage particles cannot be recovered from infected bacteria during the first half of the latent period. Once inside, the non-membrane material, now called "vegetative phage," multiplies. If the cell has been initially infected with two or more genetically marked phages,

<sup>1</sup> This review covers the period January 1, 1952 to May 30, 1953.

<sup>2</sup> The following abbreviations are used in this chapter: DNA (desoxypentose nucleic acid); FA (filterable agent).

recombination of genetic determinants (genes) occurs. This is believed by Visconti & Delbrück to result from random pairwise "mating" of vegetative particles, an event which becomes frequent after a high density of particles has been produced by multiplication. A particle is not restricted to a single mating but may undergo several matings, or none. Soon after mating starts, a process of random sorting-out and maturation of vegetative phage particles begins. Maturation consists in the conversion of vegetative into infective phage, including the acquisition of the protein coat. Maturation is an irreversible process in the host cell, and it proceeds at a constant rate. On the average, mature particles have undergone five rounds of mating. A phage cross, on this theory, is thus a problem in population genetics in which the results of single matings cannot be studied directly. Otherwise, the picture is distinctly Mendelian, involving genes, segregation, recombination, and linkage.

The above picture has little in common with an earlier theory, reviewed in previous articles in this series, according to which the phage particle breaks up into genetic subunits which multiply independently of each other and finally reassemble to form complete phage. This hypothesis has been reexamined by Dulbecco (8) and found incapable of accounting for the phenomenon (multiplicity reactivation of ultraviolet inactivated phage) which it was originally designed to explain.

For further information on the genetics and physiology of bacteriophage the reader is referred to the symposium papers mentioned above.

*Viruses of higher organisms.*—Burnet *et al.* (9) have obtained genetic recombination between two pairs of alternative characteristics in influenza virus. The authors decline to speculate on the mechanism of the interaction, except to state that simple mutation is excluded.

#### BACTERIAL GENETICS

*Genetic mechanisms.*—A new mechanism of genetic exchange has been reported in *Salmonella* by Zinder & Lederberg (10). It consists of the transfer of genetic material from cell to cell through the mediation of a particulate, filterable agent (FA). Exposure of *Salmonella* to FA from another strain induces heritable transformations ("transductions" is the term favored by the authors) in the exposed cells. A variety of characters has been transformed, including nutritional, fermentative, drug resistance, and antigenic traits. Although only a single character is transformed at a time, the possibility that FA acts as a nonspecific mutagen is ruled out by the fact that the transformations are limited to the characteristics of the cells from which the FA is derived. The most plausible hypothesis is that FA is a temperate (i.e., nonlytic) phage to which bits of genetic material from the host cell may adhere and by which they may be transferred to other cells. The *Salmonella* system thus resembles both the well-known transforming principles of *Pneumococcus* and the phages.

As a result of the work of Lederberg & Tatum, Newcombe, Rothfels, and

others, it has been generally thought that genetic recombination in *Escherichia coli* K-12 can be accounted for on the basis of regular zygote formation and meiosis, although it is necessary to assume highly irregular chromosome pairing (or, alternatively, strong negative interference) in order to make sense of the genetic data (11). This concept has now been challenged by Hayes (12, 13, 14), who has found evidence that recombination in *E. coli* involves a unidirectional transfer of genes from one parent (called F+) to the other (F-). F+ cells are distinguishable from F- cells on the following criteria: (a) The fertility of F+ is not affected by concentrations of streptomycin which prevent their growth, whereas F- cells lose fertility *pari passu* with reduction in viable cell count; also, the fertility of F+ is increased by doses of ultraviolet which decrease the fertility of F-. (b) The crosses F+ × F- and F+ × F+ are fertile, but F- × F- is sterile. (c) In crosses between F+ and F- the F- parent invariably makes the greater contribution to the genotype of the progeny.

Hayes interprets these findings to mean that F+ represents an infectious, nonlytic agent which can become associated with a part of the genetic material of the cells it inhabits and thus act as a vector in the transfer of genes from F+ to F- cells. Watson & Hayes (47) consider it likely that F+ transfers intact chromosomes, of which they have provisional evidence for three. The Hayes interpretation brings *E. coli* genetics into line with the *Salmonella* system described above. One difference is that F+ is not readily separated from the cells, so that, unlike FA,<sup>2</sup> its transmission requires cell-to-cell contact. Cavalli, Lederberg, & Lederberg (15) are in agreement with Hayes on the essential facts, but they prefer to consider F+ and F- as sex compatibility states, the former of which is transmissible by means of the virus-like agent, F. They reject the idea that F is a carrier of genetic material. The fact of unequal genetic contributions of the two parents they explain as resulting from chromosome elimination on the F+ side. They admit, however, that zygote formation has not been proven in *E. coli* and that existing chromosome maps may be invalid.

*Other transformations.*—Alexander & Leidy (16) have continued their investigations of transformation in *Hemophilus influenzae* with a report on the induction of streptomycin resistance by an extract from a resistant strain. In another study (17) they present evidence for interaction between transforming agents from different strains to produce a new type of cell. Zamenhof *et al.* (18) have shown that DNA is an essential constituent of the active principle.

*Origin of bacterial variants.*—A new approach to the problem of whether the acquisition of resistance to phage and antibiotics is spontaneous or induced has been devised by the Lederbergs (19). Their method differs from previous ones in that it makes it possible by a simple technique to isolate the mutants before they have come into contact with the agents. Induction is ruled out in these cases, in agreement with previous analyses. Ryan (20) has concluded that the adaptation of a strain of *E. coli* to grow on lactose

results from selection of spontaneous mutants. Eagle *et al.* (21) consider that the slightly enhanced resistance which develops in bacteria exposed to low concentrations of antibiotics may result from induction. Some new methods in connection with the selection of resistant mutants have been described by Bryson & Szybalski (22). They reiterate earlier findings that resistance to most antibiotics is acquired in steps, leading to the therapeutically interesting conclusion that antibiotics will usually eliminate all members of a bacterial population if used initially in high concentrations. Yudkin (23) has devised a theory called "clonal variation" to explain the acquisition of drug resistance; stated in qualitative terms, it appears to differ from existing theories, but it seems likely that further elaboration will show that it is indistinguishable from a spontaneous cytoplasmic mutation hypothesis.

*Induced mutations in bacteria.*—Demerec and co-workers (24, 25) have carried out further studies on the phenomenon of delayed appearance of mutations. They had previously shown that up to 12 cell divisions may be required following ultraviolet treatment of *E. coli* before the rate of mutation to phage resistance returns to its normal value. They now find a delayed appearance of induced reversions to nutritional independence following treatment of amino acid deficient mutants with ultraviolet or manganous chloride. They consider that the most plausible explanation of the effect is the induction of a gene instability which may persist through a number of cell divisions. The same authors have reported a new phenomenon, "mutagen stability," referring to the failure of mutagens to increase the rate of reversion of certain amino acid deficient mutants over the spontaneous rate. Finally, they have found considerable evidence that mutation in *E. coli* is intimately connected with cell division, in apparent contradiction with earlier results of Novick & Szilard which indicated a constant mutation rate per unit time, but in agreement with conclusions from the genetics of higher organisms. [See also Witkin (46)].

Newcombe (26, 27) is of the opinion that none of the mechanisms which have been proposed to explain the delayed appearance of ultraviolet-induced, phage-resistant mutants in *E. coli* are satisfactory and suggests that a systematic selection artifact is responsible for the phenomenon. With respect to the apparent discrepancies in the measurements of mutation rates, mentioned above, he suggests that these can be resolved by the hypothesis that mutation results from an error at the time of gene duplication, with the additional assumption that the probability of occurrence of an error is determined by the concentration of a chemical substance produced in the cell. That chemical substances may in fact be partly responsible for spontaneous mutations is supported by the finding of Novick & Szilard (28) that the spontaneous rate of mutation to phage resistance is reduced by one-half to two-thirds in *E. coli* when the medium is supplemented with guanosine.

Adelberg & Myers (29) have described a new, very efficient penicillin technique for the selection of biochemically deficient mutants of *E. coli*.

GENETICS OF *Neurospora* AND OTHER ASCOMYCETES

Genetically, *Neurospora* is much more like the higher plants and animals than it is like the bacteria. There is no evidence that transforming agents of either the *Pneumococcus* or *Salmonella* type have a role in *Neurospora*, although the synthesis and resolution of heterocaryons should provide an ideal means of detecting them. The fact that none have been found by this method suggests that they are rare or nonexistent in *Neurospora*, or else that they are formed as a result of cell breakage and exist only in lysates.

*Cytoplasmic inheritance.*—A case of cytoplasmic inheritance in *Neurospora* has been described by Mitchell & Mitchell (30). The character, called poky, is transmitted to all ascospores formed in poky perithecia and to few or none in nonpoky perithecia. The evidence is such as to remove any reasonable doubts as to its cytoplasmic nature. Phenotypically, poky is characterized by its slow growth rate. Biochemically, it has been found by Haskins *et al.* (31) to be deficient in cytochromes-*a* and *b* and in cytochrome oxidase and succinic oxidase activity. Young cultures contain an excess of cytochrome-*c*. Biochemically and genetically, poky resembles to a marked degree the *petite colonie* mutation in yeast, studied by Ephrussi and co-workers.

It is an interesting and possibly significant fact that the two most widespread porphyrin systems, the chlorophyll and cytochrome systems, have been found to have cytoplasmic components in their inheritance. This of course does not exclude chromosomal components also; and, in fact, chromosomal genes are known to affect both systems.

*Suppressors.*—Yanofsky (32) has reported a mutation which suppresses a tryptophan-requiring strain lacking the enzyme necessary for the synthesis of tryptophan from indole and serine. The suppressed mutant grows on minimal medium and produces the enzyme (about 5 per cent as much as wild type). The most interesting point is that the suppressor does not suppress another tryptophan mutant also lacking the tryptophan-synthesizing enzyme. The second tryptophan mutant behaves as an allele of the first in crosses and in heterocaryon tests. It can be concluded that the action of the suppressor may not be simply to take over the function of the normal allele of the suppressed mutant. Rather, it may be supposed, the suppressor partly restores to the mutant allele, or to its product, the ability to function, presumably by altering some critical factor in the intracellular environment [Horowitz (33)]. Since the extent to which the system can be reactivated will depend on the amount and kind of damage which it has suffered, it is easily understood, on this theory, why a suppressor may affect only certain alleles at a locus. This interpretation is supported in the particular case under discussion by the fact that the suppressor of tryptophanless has a deleterious effect on the growth of wild type.

Mitchell & Mitchell (34) have tested a suppressor of pyrimidineless against a number of mutant genes of the proline-ornithine and lysine series in *Neurospora*. They find that the suppressor can interact with the mutants

in various ways, sometimes acting as a suppressor, sometimes as an enhancer of the phenotype.

It is not necessary to assume that all suppressors act in the same way. Lein & Lein (35) have evidence that a suppressor of three nonallelic acetate-requiring mutants acts by opening a secondary pathway of acetate synthesis.

"Grigg effect."—Grigg (36) has found that growth of conidia of wild type *Neurospora* on sorbose-minimal medium is inhibited if the plates are heavily seeded with mutant conidia. He pointed out that this could invalidate the much used back-mutation method for assaying mutagenic activity. Grigg's conclusion was disputed by Kölmark & Westergaard (37), who pointed out that the conditions of Grigg's experiments (the use of a sorbose medium to produce colonial growth) were not the same as those of the back-mutation test (standard medium, with a genetically colonial strain). Under the latter conditions, it was reported, no "Grigg effect" was observed. Stevens & Mylroie (38), however, in a fairly extensive series of trials, obtained the effect under the standard conditions of the back-mutation test, but not with all mutants. Their results suggest that an essential condition of the phenomenon is that the mutant conidia be capable of surviving on minimal plates for prolonged periods; conidia from some strains die out rapidly and do not give the effect. Stevens & Mylroie failed to confirm Grigg's claim that the back-mutations picked up in the standard test are entirely of spontaneous origin. Jinks (39) has suggested that the "Grigg effect" is responsible for the disturbed linkage relationships observed in *E. coli*, an idea which Ryan (40) disputes on technical grounds. In any case, the discrepancies referred to by Jinks seem much better accounted for on the basis of the F-mechanism described earlier.

*Pseudo-wild types.*—Mitchell *et al.* (41) have found that the phenotypically wild progeny derived from crosses between closely linked mutants in *Neurospora* are frequently not genotypic wild types, as shown by the fact that both original mutants segregate out in crosses to true wild types. Considerable evidence indicates that these pseudo-wild types originate as disomics formed by occasional nondisjunction during meiosis. The disomic condition is apparently unstable in mitosis, so that pseudo-wild type cultures are heterocaryotic, containing haploid and possibly some disomic nuclei. This discovery is obviously important in connection with crossover or pseudoallele studies in *Neurospora*.

*Other Ascomycetes.*—Following on the successful production of diploid *Aspergillus* by Roper (42), Pontecorvo *et al.* (43) have managed to carry out a genetic analysis of the asexual species, *Aspergillus niger*. They take advantage of the fact that the diploidized strains undergo somatic crossing over. A review of *Aspergillus* genetics, containing many previously unpublished data, has appeared (85).

Lindegren (44) has presented a statement of his views on the nature of the gene. Roman & Sands (45) show that diploidization occurs spontaneously in haploid clones of *Saccharomyces* and that the diploid cells can give

rise to triploid and tetraploid zygotes. These could easily yield the aberrant ascospore ratios on which Lindgren bases his system.

#### GENES AND ENZYMES

Examples of mutations which can be shown by direct analysis to lead to a deficiency of specific enzymes have multiplied in the period under review. In addition, two cases have been reported in which a genetic change has produced a qualitative modification of enzyme structure. In following this work it is well to bear in mind that the term "mutant" is an ambiguous term covering any inherited change, whether of nuclear or cytoplasmic origin and whether genic or chromosomal. In bacteria, despite recent advances, it is not known to what extent these distinctions are valid, and in most of the biochemically important bacterial mutants no genetic analysis has been done or is feasible. On the biochemical side, it should be pointed out that what appears to be an enzyme deficiency may actually be an enzyme inhibition, or even an artifact resulting from destruction of the substrate by some competing system. These sources of error can be, but are not always, controlled.

*E. coli*.—Maas & Davis (48) have investigated the enzymatic synthesis of pantothenic acid in extracts of wild type and two mutant strains of *E. coli*. Whereas the wild type extract catalyses a rapid synthesis of the vitamin from  $\beta$ -alanine and pantoic acid (49), one of the mutants, characterized by an absolute requirement for pantothenate, shows no enzyme activity either in extracts or whole cells. The other mutant, characterized by a pantothenate requirement only at temperatures above 30°C., produces a highly thermolabile form of the enzyme. No evidence of interaction was found when wild type and mutant extracts were mixed, indicating that the difference in stability is attributable to structural differences between the enzymes, rather than to differences in the amounts of destructive or protective agents in the extracts.

Other cases in *E. coli* include an ornithineless mutant which is deficient in an enzyme for converting N- $\gamma$ -acetyl-L-ornithine to L-ornithine, studied by Vogel (50); three lysineless mutants reported by Dewey & Work (51) to lack detectable diaminopimelic acid decarboxylase activity; four strains unable to ferment lactose, reported by Lester (52) to produce significantly less  $\beta$ -galactosidase activity than the wild type; and a mutant with a requirement for isoleucine and valine, shown by Rudman & Meister (53) to be deficient in the principal transaminase system for these two amino acids. In every case there is reason to believe that the enzymatic deficiency is the cause of the nutritional defect. The findings of Rudman & Meister are of special interest, since the isoleucine-valine mutants have for some time been regarded as having a primary block only in the synthesis of isoleucine; the valine requirement was imagined to result from an inhibition of valine synthesis by the accumulating precursors of isoleucine. Much circumstantial evidence seemed to support this view [see, for example, Umbarger & Magasanik (54)]. This concept now appears unnecessary, at least insofar as it has been applied



to the transamination step in the two syntheses. This case provides a good example of the hazards involved in basing conclusions on indirect evidence.

Leupold & Horowitz (55) have published the details of an analysis of 161 temperature mutations of *E. coli*, leading to the conclusion that the method used for detecting biochemical mutants does not selectively favor the recovery of unifunctional types to a sufficient degree to account for the high frequency of such types actually found. The results thus fail to support the view that the one gene-one enzyme relationship is an artifact based on a selected group of mutants.

*Neurospora*.—Horowitz & Fling (56) have found a pair of alleles in *Neurospora* which govern the thermostability of the enzyme tyrosinase. One of the alleles determines a thermostable form of the enzyme, the other a thermolabile form. It was concluded that a structural dissimilarity exists between the enzymes on the basis of three kinds of evidence: purification studies, a kinetic analysis of the thermal inactivation reaction, and experiments with mixtures of the two enzymes. The authors point out that no conclusions can be drawn as to the mechanism of enzyme synthesis from these results, since they are consistent both with the template theory and also with the theory which assumes that one form of tyrosinase is a precursor of the other. In a study of the properties and occurrence of *Neurospora* tyrosinase, Horowitz & Shen (57) found that the synthesis of tyrosinase is not confined to one mating type, contrary to the results of some previous workers.

Evans & Nason (58) have described a nitrate reductase system in *Neurospora*; the enzyme (or enzymes) is lacking in certain mutants unable to utilize nitrate as a source of nitrogen. Only a preliminary report is available at the present writing.

*Yeast*.—Ycas & Starr (59) have described a mutant of *Saccharomyces cerevisiae* lacking cytochromes-*a*, *b*, and *c*, and containing only traces of catalase when grown on minimal medium. Addition of glycine or protoporphyrin IX results in formation of cytochrome-*c* and catalase, but not cytochromes-*a* and *b*. Genetic analysis showed that the glycine requirement is inherited as a single gene difference, whereas the cytochrome-*a* and *b* deficiency is inherited as a cytoplasmic factor. It is concluded that the strain carries a partial genetic block in glycine synthesis, resulting in a deficit of cytochrome-*c* and catalase; and, in addition, lacks the cytoplasmic factor for cytochrome-*a* and *b* production.

More inferential in nature are conclusions drawn from experiments in which the rate of some vital activity is taken as a measure of enzyme activity. In yeast, the fermentation of carbohydrates by living cells is conveniently assayed, and a number of papers have appeared in which genetic aspects of fermentation have been studied. Several reports from Lindegren's laboratory (60, 61, 62) have dealt with the genetic control of oligosaccharide fermentations. The enzymes being investigated are presumed to be carbohydrases of various kinds. Similarly, Spiegelman & DeLorenzo (63) have studied the inheritance of the ability to ferment galactose. They conclude



that the ability to initiate production of the galactose fermentation system ("galactozymase") is inherited in a Mendelian way, but that once established in the cell the system is self-perpetuating in the presence of galactose. It is not known what component, or components, of "galactozymase" is actually involved here.

*Mammals.*—Phenylpyruvic oligophrenia, an hereditary form of feeble-mindedness in man, is characterized by the excretion of phenylpyruvic acid in the urine (phenylketonuria). Jervis (64) has carried out experiments with livers from normal and affected individuals and reports that he was unable to detect, in the affected livers, the enzyme system which converts phenylalanine to tyrosine. He concludes, perhaps prematurely, that absence of this system is the essential metabolic lesion of the disease. The fundamental work on the system was done by Udenfriend & Cooper (65). It is evidently complex, involving at least two enzymes. The mechanism of the reaction is unknown.

Foster (66) has compared the tyrosinase activity of foetal guinea pig skins of different color genotypes. He finds no simple parallelism between enzyme activity and the amount or kind of natural pigment. Some pigmented skins showed no detectable activity, and others with extremely reduced pigmentation showed relatively high levels of activity.

#### METABOLIC PATHWAYS

The application of genetics to problems of metabolism being somewhat peripheral to the main topics of this review, we shall mention only briefly some of the interesting contributions in this field.

*Neurospora.*—Bonner *et al.* (67) have obtained evidence that a number of mutants of the tryptophan nicotinic acid group are not completely devoid of the capacity to carry out the synthesis; 7 out of 9 strains tested showed evidence of incomplete blocking. Doudney & Wagner (68), on the basis of a study of a threonine-sensitive mutant, have arrived at the interesting conclusion that threonine and homocysteine may be precursors of the thiazole moiety of thiamine. Haas *et al.* (69) and Ames *et al.* (70) have analysed the pathway of histidine synthesis by use of a series of histidine-requiring mutants. The usual procedure of isolating accumulated metabolic products was followed, but none of the products (a series of imidazole derivatives) were active as biological precursors of histidine. The hypothesis was advanced, supported by some chemical evidence, that the actual intermediates are phosphate esters of the isolated compounds. Harris (71) has studied the interaction of thiamine and pyridoxin in growing mycelium and concludes that pyridoxin interferes with thiamine synthesis, whereas thiamine inhibits the destruction of pyridoxin. Harrold & Fling (72) have described mutants which require formate or formaldehyde for growth; adenine supports limited growth. Sheng & Sheng (73) have reported a study of carotenoid synthesis in a series of color mutants. Strauss (74, 75) has investigated various aspects of the metabolism of a number of acetate-requiring strains.

They accumulate acetyl methylcarbinol, leading to the conclusion that these mutants are unable to complete the oxidation of pyruvic acid.

*Glomerella*.—Markert (76, 77) has described the production of nutritional mutants in the Ascomycete, *Glomerella*. They have the convenient property of being visibly distinguishable from the parent type, making the task of selection relatively easy. Two mutants have been found which grow when supplied with glutathione, but not when given a mixture of the constituent amino acids. They grow on a mixture of cysteinylglycine and glutamylcysteine. Both mutants appear to carry chromosomal aberrations.

*E. coli*.—Davis (78, 79) has continued his important series on the biosynthesis of aromatic compounds. He deduces a branched pathway in which a derivative of shikimic acid gives rise in separate reactions to the following compounds: *p*-aminobenzoic acid, anthranilic acid, tyrosine, phenylalanine, and *p*-hydroxybenzoic acid. He points out that the results of the mutant study contradict in several points the conclusions arrived at by inhibition analysis of the same pathway. [For a contrasting view, see Bergmann *et al.* (80).] Utilizing another series of bacterial mutants, Vogel & Davis (81) have analysed the pathway of proline synthesis from glutamic acid. Maas & Vogel (82) have arrived at the interesting deduction that  $\alpha$ -ketoisovaleric acid is a precursor of the pantoic acid moiety of pantothenic acid; this means that pantothenic acid and valine have a common precursor. In the course of their investigations of the structure and function of lipoic acid derivatives, Reed & DeBusk (83) produced a mutant of *E. coli* with a requirement for acetate, citrate, and succinate. These were replaceable by a conjugate of lipoic acid, identified as lipothiamide. The mutant is unable to conjugate  $\alpha$ -lipoic acid with thiamine. Stone & Hoberman (84) have analyzed the mode of utilization of proline peptides by a proline-requiring strain. Under aerobic conditions, peptides are utilized better than free amino acids, but under anaerobic conditions peptides and free amino acids support equal growth. The authors present evidence which indicates that the effect is a result of the aerobic deamination of free proline. They conclude that peptides are not utilized in a unique manner by the mutant, but must first be hydrolysed.

#### CELLULAR ANTIGENS

Transfusion reactions and erythroblastosis fetalis have called widespread attention to the diversity of human cellular antigens, and serological research has provided increasingly sensitive techniques for the detection and study of these inherent human differences. The reviewers are faced with an embarrassment of riches in the recent contributions to this field, and only a few categories of interest can be sampled here. Perhaps the predominant conception to be gained from this consideration is the very great complexity, and the high degree of individuality, of the antigenic characteristics of cells and of the antisera by which they are recognized. This complexity has at least three aspects: numerous genetic loci contribute to the antigenic characters of cells; a considerable extent of allelic diversity has already been recognized

at several of these loci; and the antisera which define the cellular antigens are probably seldom, if ever, as sharply specific as one might wish them to be. Studies of chemically known haptens (86) have established that a multiplicity of antibodies, varying in kind and degree of specificity, are produced in response to a single unit of antigenic structure. This antibody population can be fractionated by reaction with antigens related to the one that induced their formation, but there is no necessary simple correspondence between an antibody fraction so isolated and any particular detail of structure in the antigens. The cellular antigens controlled by a series of alleles frequently display serological interrelationships. A representation of these relationships, based on a supposition that a mosaic of sharply distinct structural characteristics shared by or distinguishing the related antigens is revealed by corresponding antibody fractions of discrete and absolute specificity, is suspect because of the patently unrealistic nature of the serological assumptions upon which it is based.

The "C-D-E" conception of the Rh complex, which involves the kind of assumption mentioned above, seems especially dubious in the light of recent developments. Recognition that the three "pairs of alternatives" postulated by this conception do not in fact encompass the variations in this series of related antigens antedates the period covered by this review. Besides the necessity of substituting such series as "C-C<sup>U</sup>-C<sup>W</sup>-c<sup>v</sup>-c" for the simple alternatives C and c [see (87) for an earlier review], and other similar extensions, the retention of this conception has required the postulation of a chromosomal deletion to account for the failure of certain Rh antigens to give evidence of any property that might be assigned to the hypothetical "C or E loci" (88, 89), and the postulation (90) of still another "component," f, which has to date been noted only among antigens sharing the specificities that had been designated c and e. Meanwhile, Wiener *et al.* (91) have discovered an additional antigen which, if it were to be described by the C-D-E-F system, would require a deletion only at the "E locus." Rhesus monkey blood shows no test evidence of specific reaction with antibody fractions designated anti-C, -c, -D, or -E, but guinea pigs injected with monkey cells produce a good "anti-D" (92; see also 93). The assumptions that "D" must be present in order to induce antibodies subject to this designation, and that in monkey blood "D" is so situated in the cell that it cannot react with the antibodies, seem unwarranted because human Rh-negative cells, which by definition lack "D," nevertheless liberate on heating a substance that will also induce "anti-D" in guinea pigs (94). Ponder & Ponder (95) have suggested that the active antigen is a modified product of the fragmentation of the heated cells. Whether the material is native or is a product of fragmentation, it cannot on present evidence be identified with the hypothetical "substance D" but can only be described as a material that, on injection into guinea pigs, induces a pattern of cross reactive antibodies, including many similar in specificity to those found in anti-Rh<sub>0</sub> serum. When this heterogeneous population is fractionated by minimal absorption with Rh-negative cells, a

reagent comparable to an anti-Rh<sub>0</sub> reagent is obtained. These observations are entirely compatible with an interpretation of the Rh complex as a series of single, related antigens. They offer serious difficulties to an interpretation on the "CDEF" basis. In a paper also reporting other evidences of the complexity of isoimmunization and Rh typing, Wiener & Brancato (96) have described a variant of Rh<sub>0</sub> of unusually low avidity, which permitted the baby possessing it to display only a mild degree of erythroblastosis in spite of a high maternal antibody titer.

Coincident with the extension of the series of distinguishable Rh antigens has come a recognition of the complexity of the antisera that provide the tools for typing bloods. Cann *et al.* (97) fractionated three Rh antisera by electrophoresis convection and found Rh-reactive antibody throughout the serum globulins, including  $\alpha$  globulin. They noted marked individual variations even in sera of the same type. In addition to differences in the variety of antigens with which they will react, antibodies can be classified in terms of their effects on positive cells in particular test systems, for example, those which produce agglutination in saline diluents, or block the saline agglutinins, or cause agglutination in the presence of antiserum to human globulin, or agglutinate trypsin or other enzyme-treated cells, or agglutinate only *ir.* colloid diluting fluids, or block the antibodies that agglutinate in such systems. It has been pointed out (98) that when mixtures of these diverse antibody types are present in an antiserum, conclusions based on tests with the serum will often depend on the particular testing technique used. The competent use of a battery of these newer techniques seems likely to reduce the incidence of transfusion reactions (99, 100).

Many of the antisera that have been studied in connection with the recognition of new antigenic variants have shown complicated mixtures of antibodies. For example, serum from the original individual displaying the postulated "deletion" (-D-) contained antibody fractions described as "anti-C, anti-c, and anti-e"; and serum from another individual of the same type (89) would react with cells having the antigenic specificities labelled e and perhaps also C, c, and E. A new Rh antibody fraction called f (90) was found in the serum of a hemophilic male who had received 35 blood transfusions; his serum also contained anti-B, -K, -S, and -N. Three of the five people in whom anti-Duffy (anti-Fy<sup>a</sup>) antibodies have been reported were also hemophilic (101). The new blood group antibody recognizing Jk<sup>b</sup> (an allele of Kidd) was found in a serum also containing anti-Fy<sup>a</sup>, after transfusion and miscarriage. Clear and consistent demonstration of the anti-Jk<sup>b</sup> activity of the serum requires the use of the indirect anti-globulin test on trypsin-treated cells (102). In a study of quantitative aspects of human antigen Fy<sup>a</sup>, Race *et al.* (103) observed that trypsin-treated positive cells reacted to one serum only when homozygous, and that another antiserum detected a common dosage effect at this locus. There appeared to be some relationship between this antigen and Rh; on statistical grounds, Rh-negative people were too often Duffy-positive, and too often homozygous for the Duffy antigen.

Limitation of space forbids the discussion of numerous other studies related to the human erythrocyte antigens. Categories of investigation that have produced results of particular interest to the reviewers include additional studies of the nature and effects of Rh antibodies and of their transmission across the placenta (104 to 107); erythroblastosis-like phenomena in animals (108, 109, 110); population studies of Rh and other blood types (111 to 114); genetic and population studies of associations among various blood-cell characteristics and other human attributes (115 to 120); reports dealing with newly discovered erythrocyte antigens (121, 122, 123), and the nature of those already known (124, 125); the relationships among the Lewis antigens, the secretor characteristic, and the A-B-O blood groups (126, 127, 128); and studies of the normal blood groups themselves, with particular reference to the nature, origin, and interrelationships of the normal antibodies and the corresponding antigens in human blood (129 to 136) and of other, diverse origins, including other animal materials (137 to 141) and plant extracts (142, 143, 144).

Immunogenetic analyses of the erythrocytes of species other than man have continued to reveal extended multiple allelic series controlling antigens interrelated in ways that suggest complex patterns of cross-reaction. In the "B system" of cattle at least 80 different "blood groups" have been reported (145), each apparently controlled by an allele at the *B* locus. The "C system" includes at least 22 groups and alleles. Two other systems, at present much less complicated, have also been described (146), and there are in addition a number of apparently independent loci affecting cellular antigens in cattle. A similar situation prevails in chickens; the earlier work of Briles *et al.* (147) has been extended to a detailed study of the *C* and *D* blood group loci, both of which are complex (148). A point of considerable interest is the report by Shultz & Briles (149) that "natural" selection under flock conditions favored heterozygosity at the *B* locus, while "artificial" selection for high egg production favored heterozygotes at the *A* locus and probably at the *B* locus as well. It seems likely that at least part of the explanation for the great diversity of cellular antigens segregating in animal populations may rest on a physiological advantage conferred by heterozygosity for chromosomal regions marked by the antigen-controlling genes. Such selective conditions oppose the usual tendencies toward fixation or loss of alleles, and genetic heterogeneity is maintained. Restrictions of space prevent the citation of several other genetic studies relevant to this concept. With specific reference to immunogenetic heterozygosity, however, the recent work of Bryan & Miller (150) should be mentioned. Antisera to pigeon bloods heterozygous for a pair of contrasting characters (*C'* and *C*, found in *Columba guinea* and *Columba livia* respectively) contain an antibody fraction that will react only with the cells of heterozygotes. This provides direct serological evidence of interaction producing an effect of heterozygosity *per se*, but whether this specificity is more properly ascribed to a substance unique in the heterozygote, or to some other more subtle consequence of the nature of antibody responses and reactions, and whether the effects observed are those

of the alleles designated or of associated chromosomal regions, remain to be established. Other pairs of contrasting characters (150, 151) in the same hybrids have given no evidences of similar allelic interactions. Irwin (152) has reviewed and extended his classic studies of evolutionary patterns in pigeon and dove antigens.

Fox & White (153) have repeated and extended earlier observations suggesting that genes at different loci may interact in affecting the specificity of antigenic materials found in *Drosophila* extracts. The important work on antigens in paramecia has included a report by Beale (154) of three loci affecting antigen variation in *Paramecium aurelia*, var. 1. Four alleles have been recognized at the *g* locus, three at *d*, and two at *s*. Antigens controlled by alleles usually display a serological relationship. Only one of the three loci is normally expressed in an individual at any particular time; which one is detectable depends on the cytoplasmic state of the cell, and the stability of these alternative states varies widely. Transformations occur when the temperature of culture is changed; these often show a prolonged delay, but the transformations when they occur are sudden.

Numerous papers in the field of bacterial, bacteriophage and virus serology must be neglected here.

#### TRANSPLANTATION SPECIFICITY AND RELATED PHENOMENA

The establishment of permanent natural transplants of hematopoietic tissue exchanged between twin bovine embryos (155, 156) has been subjected to further interesting study by Stormont *et al.*, working with cattle (157) and sheep (158). In both, the exchange is associated with freemartinism when the embryos differ in sex, but in a recent report by Dunsford *et al.* (159) of a human female erythrocyte chimaera evidently illustrating the same phenomenon, whose twin had been a male, no sexual abnormality existed. The report offers several other points of interest: for example, the male twin, who had died 25 years ago at the age of three months, could still be blood-typed because descendants of his cells comprised almost 40 per cent of his sister's erythrocyte population. Although the chimaera had in her circulation large numbers of A cells derived from her twin, her behavior as a secretor was consistent with her own tissue-genotype, and she secreted O (H) substance in her saliva, not A. Contrasting with this tissue-specific aspect of the physiology of secretion, the presence of normal antibodies in her serum was affected by the nature of the circulating cells; the chimaera was genotypically of blood group O, but no anti-A was present in her serum. The authors minimize the possibility that anti-A was being formed but constantly being absorbed by descendants of the transplanted A cells, on the grounds that the circulating A cells gave no evidence of sensitization in delicate test systems. However, the work of Anderson *et al.* (160) and Billingham *et al.* (161) on skin transplants in twin cattle suggests that cells or materials other than erythrocyte primordia are also involved in the twin embryo exchange; if so, it is conceivable that anti-A formed by the human



chimaera might be reduced below detectable levels by other tissues. Alternatively, the histocompatibility work of Snell *et al.* (162, 163) supports earlier suggestions that the presence of large amounts of antigen "paralyzes" the antibody-producing mechanism in some little-understood fashion; on these grounds the absence of anti-A in the chimaera might well represent a more fundamental effect than one of simple absorption. The autonomous nature of the A and O properties of the chimaera's erythrocytes suggests that this antigenic alternative is inherent in the blood cells and is not a secondary characteristic derived from other tissues, as was found by Stormont (164) to be true of a cattle antigen recognized by means of normal isoantibodies. The papers by Snell *et al.*, cited above, include an admirable study of the genetic control of transplant specificity in mice, involving, as with erythrocyte antigens, complex multiple allelic series with evidences of cross-relationship among the active products of alleles.

Ripley & Owen (165) have produced persistent erythrocyte mosaicism by injecting embryonic rat cells into rat embryos of different blood type. Andres (166) has injected dissociated cells from particular chick embryos into the circulation of other embryos and reports that teratomas of various composition are formed by the donor cells in the host embryonic membranes. These and earlier observations by Weiss & Andres (167) suggest that donor cells also participate in a type-specific localization within the embryonic host and are incorporated into its normal differentiation. Evidence on this latter important point appears at present to be restricted to pigment cells; the parallelism with the natural twin chimaeras and with the experimentally produced rat mosaics is, however, striking. Chiakulas (168) reports that in amphibia intimate host-graft fusion occurs only between tissues normally associated in an intact organism; such tissue-specific cell affinities tend to support the conception of organization described by Weiss as "molecular ecology." Prehn (169), however, reports that tumor transplants into skin grafts indicate no intrinsic incompatibility between fixed tissue of different genetic origin; these incompatibility reactions appear to be systemic rather than local interactions between dissimilar, adjacent tissues. Smith *et al.* (170) report that virus-induced rabbit papillomas grow well when transplanted to suckling young, in contrast with their uniform failure when transplanted to adults. Space is too limited here to permit reference to numerous other studies of tumor transplantation.

#### OTHER GENETIC CHARACTERISTICS OF PHYSIOLOGICAL INTEREST

**Hemoglobins.**—Great interest attaches to the recognition that human hemoglobin is subject to straightforward genetic modification. Several recent reviews [e.g., (171 to 174)] have dealt with this material and permit presentation of a general picture here without separate citation or discussion of the numerous original papers. Two systems of hemoglobin synthesis are recognized, one leading to the formation of fetal hemoglobin (F) and the other, replacing the first during normal development, leading to normal adult

hemoglobin (A). F and A are sharply distinct, particularly in terms of their serological specificities (175, 176) and their susceptibility to alkaline denaturation. Either a genetic block to the synthesis of A (exemplified by the allele for thalassemia) or environmentally induced anemia apparently leads to the maintenance or reactivation of the fetal mechanism, so that the hemoglobin of individuals homozygous for thalassemia is indistinguishable from F. Anemic individuals often have some F in addition to A, and serological evidence has suggested that even individuals classified as normal adults may have small amounts of F (175). The adult mechanism is subject to several genetic deviations; the most frequent of these is effected by the sickle-cell allele, responsible for the formation of an electrophoretically distinguishable hemoglobin (B). The cells of heterozygotes sickle and contain both kinds of hemoglobin, the quantity of A predominating over that of B. Homozygotes are sickle-cell-anemics and have B but no A; they usually also have varying amounts of F presumably resulting from a compensatory reactivation of the fetal mechanism like that found in other types of anemia. The relative amounts of B and A in sickle-cell heterozygotes vary in different individuals; this quantitative variation appears to have a strong genetic component, but its basis is at present uncertain. Itano (177) has presented evidence that "isoalleles" of the normal alternative may differ in their efficiency in competition with the allele governing hemoglobin B synthesis. The allele for thalassemia is clearly not at the sickling locus; it nevertheless evidently provides a more complete block to the synthesis of A than of B, since doubly-heterozygous individuals (for sickling and thalassemia) show a predominance of B over A, together with varying amounts of F (178). An explanation consistent with these data would place the block effected by the thalassemia allele after the point at which the sickling locus acts. It seems possible that a sequence of gene-affected reactions in the synthesis of hemoglobin may emerge from future work along this line. Meanwhile, additional abnormal adult hemoglobins (C, D) have been shown to be simply inherited. The genetic relationships among the aberrant adult hemoglobins have not been definable by the data at hand; more general biochemical-genetic considerations might suggest the hazardous guess that an extended multiple-allelic series, including several alleles giving qualitatively aberrant products as well as those resulting in essentially quantitative variations (the normal isoalleles), is involved. The genic action in the synthesis of aberrant hemoglobins seems clearly to affect the synthesis of the globin, not of the heme (179, 180). Population studies of the sickling characteristic offer some challenging problems (181 to 185). Somewhat related papers of genetic interest dealing with hemoglobin in sheep (186) and in mice (187) might well be singled out for specific mention, from among the numerous papers at hand.

*Hemophilia.*—The general term "hemophilia" has been shown to include several different disorders, primarily by the application of a technique familiar in biochemical genetics. Plasma or serum from one hemophilic individual may restore the clotting property to plasma of another; it follows that different components of the clotting system are deficient in the two individuals.



At least three plasma thromboplastin factors account for at least three types of hemorrhagic disease (188): absence of AHG (anti-hemophilic globulin) is corrected by barium sulfate treated normal plasma but not by serum; absence of PTC (plasma thromboplastin component) is corrected by normal serum but not by barium sulfate treated normal plasma; and PTA (plasma thromboplastin antecedent) deficiency is corrected by either of the materials mentioned. Several papers (189 to 194) have dealt with these and perhaps other hemophilia-like disorders and their bases. Genetic data are at present insufficient to ascertain how these deficiencies are related in inheritance or, in fact, whether some of them are inherited at all. Methods currently at hand do not appear to be sufficiently sensitive to detect the relatively slight clotting defect which may be characteristic of female carriers of traditional hemophilia (195). There has, however, been reported a case of true hemophilia in a woman (196). Circulating anticoagulants that appear after repeated transfusion of hemophilic persons have been subjected to further study (197, 198); the specificity of this apparently immune response may in the future provide additional tools for the identification and study of genetic variations in this class of disorders.

*Other physiological traits.*—An apparent homozygote for the Pelger-Hüet anomaly of leucocytes has been described (199, 200). Although the nuclei of granulocytes were like those in rabbits displaying a very similar anomaly, the condition is evidently not lethal when homozygous in man, as its prototype is in rabbits. Hereditary spherocytosis has been shown to depend upon a Mendelian dominant; the characteristic shows a higher incidence in men than in women and appears to be associated with leg ulcers and gallstones (201). The inheritance of oval erythrocytes, and possible linkage with other blood factors, has been reported by Bird & Bailey (202). An extensive study of the genetics of diabetes mellitus (203) has led to the conclusion that a simple autosomal recessive is responsible for this disorder. The frequency of the recessive allele is estimated to be between 0.2 and 0.25. A simple recessive, fully penetrant, is believed to be responsible for fibrosis of the pancreas (204). The disease is rather frequent (0.7 to 1.0 per 1000 live births), and either a high mutation rate or some degree of superiority of the heterozygote is postulated as a basis for this high frequency. The reader is referred to the excellent bibliographies published in each issue of the *American Journal of Human Genetics* for further citations of human genetic studies of physiological interest.

We must neglect many interesting reports of genetic studies in other animals and in plants, but reference should be made to the publication of the second edition of Grüneberg's *Genetics of the Mouse* (205). The book presents and explores numerous important physiological and developmental facets of its subject. Heston (206) has reviewed the relations of mouse genetics to our understanding of human cancer.

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## COMPARATIVE PHYSIOLOGY OF NERVOUS SYSTEMS AND SENSE ORGANS<sup>1</sup>

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This review deals with the strictly comparative aspects of the physiology of nervous systems and sense organs; it does not consider mechanisms of excitation of nerve or of stimulation in sense organs, nor does it consider theories of conduction in axons or of transmission at synapses; it does not consider animal behavior *per se*. Only a few references prior to 1950 are included; some of the topics of this review were summarized in (1, 2). Buddenbrock's important book on sensory physiology (3) appeared during the period of this review and aspects of the subject dealing with insects are considered in (4). There are also pertinent papers in the Symposium of the Society for Experimental Biology (1950) and in the Cold Spring Harbor Symposium (1952).

### NERVE NETS

Nerve nets constitute the major portion of the coordinating nervous system in coelenterates, enteropneustans, and many echinoderms; nerve nets may be important in peripheral motor coordination in some annelids and molluscs, and they provide for local integration in visceral musculature in animals of many phyla. Pantin and co-workers are continuing to analyze the structure and function of nerve nets in sea anemones and medusae (see 5, 6). Photographs in (6) demonstrate that the net synapses are continuous, with equal surfaces of neurones in apposition, providing ample area for two-way conduction. Conduction tracts may be through and fast or diffuse and slow. In a mesenteric net of *Metridium* there are more than 20 synapses in a 5 cm. tract through which conduction requires only 50 msec., hence the calculated delay per junction is certainly less than 2.5 msec.; no delays and fiber velocities have been measured directly, however. If the nerve net is taken as the primitive nervous system, facilitation is the basic rule. The column of *Metridium* requires a series of stimuli at intervals of some three sec. to elicit a response; efforts to extract an agent responsible for neuroneural facilitation failed although earlier indications were that tyramine might be effective (7). Not all net junctions require facilitation, however, and in the first action potentials recorded from individual coelenterate nerve fibers a single impulse is found per beat of the bell of *Aurelia* (8). Intact anemones in darkness show spontaneous rhythms and varied patterns of behavior, some extremely slow; apparently some cells in the nerve net may be capable of innate rhythmicity (9). With extended use of electrical recording the

<sup>1</sup> The survey of the literature pertaining to this review was concluded in June, 1953.



"primitive nervous system" may prove to be very complex. Pantin (5) suggests that with neurones only  $100\mu$  long, as in *Hydra*, electrotonic spread of local potentials might be sufficient for activating successive neurones, but it is difficult to see how this would permit self-propagation.

The subepidermal net in the enteropneustan, *Saccoglossus cambrensis*, is adequate for some coordinated responses although it is regulated by the nerve cord in the proboscis (10). In the ascidians, *Phallusia* and *Ascidella*, facilitating responses via the peripheral net continue after deganglionation (11); in *Ciona* the central ganglion may have more control (12). In starfish, stimulation of epidermal sense cells can result, depending on stimulus strength, in localized responses via a peripheral net, in spread by segmental or by extrasegmental nerve arcs, or in distant responses involving the radial nerve cord, i.e., peripheral reflexes or central generalized responses (13).

#### Giant Fibers and Their Synapses

A sufficient number of single synapses have now been analyzed to indicate a series of varying complexity. Bullock (14) suggests that facilitating synapses are more general and more primitive, whereas one-to-one transmission represents a high degree of specialization, and his classification from more complex to simpler synapses is useful. Most complex are the giant fiber junctions in the abdominal ganglia of the cockroach [summary by Roeder in (4)]; these are polarized, show much lability of response pattern, and both spatial and temporal facilitation.

Next in decreasing integration are the polarized synapses which normally conduct one-to-one but which can be made to facilitate. The synapse between second and third order giant neurones in the squid stellate ganglion is a well-known example. Recent studies of the giant fibers of the crayfish show differences in detail from the squid synapse. The two lateral giant trunks consist of segmental giant neurones which synapse (a) with sensory elements in the neuropile, (b) with the partner neurone at a crossing of the cell processes, (c) with the lateral giant of the next posterior segment, (d) with motor elements of roots of the next anterior ganglion, and (e) with the giant neurone of the next anterior segment (15). The two median giant fibers, on the other hand, originate in the brain, decussate, and run the full length of the nerve cord to the telson. The fibers of the motor root neurones can be activated by the homolateral giant or by either median one, as well as by fibers from another root of the same ganglion (16). The pattern of the motor synapses differs slightly for different roots but, in general, conduction is one-to-one until fatigue sets in, after which facilitation is required. Records from the second root of abdominal ganglia may show, in response to a single impulse in a median giant fiber, one large spike and then a repetitive series of small spikes at a frequency as high as 300 per sec. (15, 17). The motor fiber synapse is most sensitive to anoxia, the lateral giants less and the median giant fibers least sensitive (18). The motor synapses can be blocked by ery-



throidine but the giant fibers are unaffected (19). In another decapod crustacean, *Callianassa*, either of the pair of giant fibers can activate a motor root fiber but in the telson more motor fibers are activated by the homolateral than by the contralateral one (20).

The next level of decreasing complexity in the single synapses is in the one-to-one nonpolarized junctions. For example, the junctions between successive lateral giant neurones in the crayfish are not polarized, are one-to-one, but in fatigue can be facilitated. In *Callianassa* the two giants (corresponding to the median ones of the crayfish) synapse in the brain and if one is stimulated, an impulse is reflected in the other with a delay of less than 0.5 msec. (20). In the polychaete worm, *Protula intestinum* (21), similar reflection occurs, the junction following at as high frequencies as the fibers (160/sec.); these junctions can be blocked by fatigue but not facilitated. Another worm, *Spirographis*, shows numerous points of decussation of the giants in the body region and on fatigue the crossing shifts toward more anterior decussations (21). The morphology of giant neurones in the related worm, *Branchiomma*, has been described (22).

The simplest type of synapse is at the septa of giant fibers of certain annelids such as *Lumbricus* and *Nereis* (23). These septa usually show no delay, no polarization or fatigue block (14); however, in *Megascolex* conduction is two-way in the giant fibers, but after fatigue, conduction continues longer in the "normal" than in the antidromic direction (24).

There is little doubt that giant fiber systems, whether composed of successive giant neurones or of a single long neurone, have survival value for quick reactions. However, their main advantage is in the synchronous activation of a large area of musculature. With increased fiber diameter in giant fibers the velocity is increased less in proportion than is the size of the action potential (14). In *Protula* and *Spirographis* there may be interaction with variable latency between the giant fibers in the body where no decussations occur, perhaps as a result of electrical spread at a distance (21).

Electronmicrographs of the synapses between the median giant and the third motor root neurones of the crayfish and of the synapse between second and third order giants of the squid show processes of the post-synaptic neurone which penetrate the presynaptic sheath so that the two axolemmal membranes are double but closely adhering (25). Bodian figures synapses of vertebrates as a series of histological types: spiral and basket endings, boutons, axo-axonic apposition junctions, and club-like endings (26).

Giant nerve cells have been described in *Saccoglossus* (10), in *Lingula* (27), in nymphs of *Anax* (28), and in *Locusta* (29).

#### SMALL-FIBER INTEGRATION SYSTEMS

*Invertebrate ganglia.*—The single synapses of giant fiber systems of invertebrates have been so useful for studying transmission mechanisms that little attention has been paid to the small-fiber systems in which most inte-

gration occurs. Bullock (14) points out that most neurones in invertebrate nervous systems are unipolar, hence dendrites are absent, and junctions are from axon to axon. Ganglionic transmission which does not involve giant neurones but which is relay in character has been described in the pedal ganglion of the slug, *Ariolimax columbianus* (30, 31). The same postganglionic response can be elicited by any of three converging and summing pathways; ganglionic delay is 33 msec. at 7.5°C. and 19 msec. at 21.7°C.

Control of posture in the cockroach by thoracic ganglia is postulated as resulting from electrotonic potentials in interneurones near motoneurones; supporting this is the observation that with transverse DC polarization of the ganglia the leg on the cathodal side flexes and on the anodal side extends (32). The pacemaker cardiac ganglion of *Panulirus* receives both accelerator and inhibitor nerves and either effect requires facilitation (33). Sheathed nerves and ganglia contain a red pigment in the clam, *Macra* (34).

The neurological basis for complex behavior in the octopus provides evidence for the importance of feedback connections in memory (35, 36). One specific circuit is: optic lobes → lobus frontalis → lobus verticalis → lobus subverticalis → optic lobes. Removal of the superior frontal or verticalis lobes from the cerebral mass abolishes training; however, there may be short-term association and related behavior as long as the signals of an image persist in the optic lobe. The "higher centers" permit generalization among different sense modalities and retention of habits for at least two days in the absence of persistent images.

A new type of nervous structure in crustaceans has been discovered by Alexandrowicz (37, 38, 39). The stomatopods have unpaired median nerve trunks between the paired longitudinal connectives. These median connectives give off nerves of which some fibers supply the alary muscles of the pericardium and others innervate one wall of the dorsal blood sinus. In the sixth thoracic segment, fibers from this system form a neuropile-like organ across the blood sinus. The function of this strange structure is unknown.

Rhythmic nerve centers are indicated in the polychaete *Arenicola marina* by observations of behavior (40, 41, 42). The pumping movements which irrigate the worm's tube depend on pacemakers in the ventral nerve cord whereas the feeding cycle depends on nerve elements in the proboscis-oesophagus. In *Arenicola ecaudata*, which lives between stones rather than in tubes, there is little evidence for an oesophageal pacemaker, but rather the extrovert is more subordinate to the brain (42).

*Lower vertebrates.*—The mesencephalic optic lobes (tectum and tegmentum) of fishes and amphibians have resemblances to the cerebral cortex of mammals. In the catfish, *Ameiurus nebulosus*, an optic tectum gives both fast and slow electrical responses to stimulation of the optic nerve (43). Strychnine fails to augment this response (44); local stimulation of the retina results in corresponding localization in different parts of the contralateral optic lobe (45). Vagal and facial lobes are larger in fish which are mouth or skin tasters than in fish which are predominantly sight feeders (46).

In larvae of *Amblystoma* the spinal cord can coordinate swimming up to a certain stage of development, thereafter the midbrain is essential for swimming although the medulla modulates motor centers in the cord, and the forebrain has little effect on swimming (47). In anurans, particularly *Bufo marinus*, local stimulation of the midbrain shows motor representation of various body regions, and injury to this part of the brain causes profound motor disturbances (48). For diagonal ambulatory movement a toad needs both roots of at least one spinal segment; standing requires proprioceptive afferents (49).

In reptiles the forebrain gains importance, and in lizards, removal of the forebrain resulted in diminution of spontaneity, burrowing, and of recognition of food and water (50).

The pattern of spontaneous electrical activity shows similarities in all classes of vertebrates. In the medulla of the carp, unit spikes were found in the respiratory center associated with gill movements and in the acoustic tubercles in response to sound, but not in vagal and facial lobes (51). Rhythmic waves, 6 to 7/sec. were recorded from the surface of the forebrain of the frog; these waves were greatly enhanced by stimulation of the thalamus, slightly enhanced by optic lobe stimulation, and reduced but not abolished by cutting thalamo-cortical tracts (52). Brain waves from cat, hedgehog, and mole were compared (53), and in the opossum pathways apparently connect the two hemispheres by way of the tegmentum (54).

Hibernating mammals are poikilothermic, and ground squirrels asleep at body temperature of 5°C. show no brain waves, but at 8°C. they show occasional bursts of electroencephalogram activity (55). Hamsters, however, show no brain waves at body temperatures below about 19°C. (56). Woodchucks (*Marmota*) show occasional spontaneous activity at 11°C. and responses to sound at 7°C. (57). Although their brain waves show species differences, the nervous system of hibernators retains its coordinating capacity at temperatures far below lethal for nonhibernators. A different sort of response to cold is found in leg nerves of cold-acclimated herring gulls in which conduction in the metatarsal portion of the nerve stops at 2.8 to 3.9°C. whereas the tibial portion of the same nerve is blocked at 11.7 to 14.4°C. (58).

The morphology of the autonomic nervous system of a chimaeroid fish has been described (59), and the autonomic systems of lower chordates has been reviewed (60). The general pattern of parasympathetic and sympathetic systems, despite detailed differences, is surprisingly similar in all vertebrate classes.

#### CHEMICAL MEDIATORS IN NERVOUS SYSTEMS

The function of acetylcholine (Ach) in the central nervous system of arthropods remains unknown. Ganglia of the crab *Carcinides* contain acetylcholine esterase, choline acetylase, but liberate no more Ach when stimulated than at rest (61). Cholinesterase is much higher in concentration in the

*Carcinus* than in the frog nervous system (62), and Ach is synthesized by extracts of crayfish nerve cords (63). In giant fiber synapses of *Callinassa*, eserine and Ach are without effect, but nicotine and di-isopropyl fluoro-phosphate (DFP) block (64).

In bee brains the cholinesterase concentration closely parallels the neurone cell number (65), and in several insects the pattern of hydrolysis of different substrates indicates differences between insect cholinesterases and the corresponding enzymes from both serum and nerves of vertebrates (66). After 1,1,1-trichloro-2,2-bis(*p*-chlorophenyl)-ethane (DDT) prostration of the cockroach, free Ach increases greatly in the nerve cord (67).

Extracts of sensory nerves and sensory centers yield an active vasodilator agent, different from acetylcholine and histamine; strychnine and picrotoxin are said to protect this "sensory substance" from enzymatic destruction (68). This "sensory substance" is found in a wide variety of animals other than vertebrates, such as arthropods, echinoderms, molluscs, but not in annelids and coelenterates (69, 70). However, different methods of extraction demonstrate the same material in ventral as well as dorsal roots; strychnine protects only at high concentrations, hence the existence of a "sensory substance" is seriously questioned (71).

#### PHOTORECEPTORS

In a series of papers (72, 73, 74) Autrum has examined the electroretinograms of many insects. One group, consisting of such insects as *Dixippus*, *Periplaneta*, *Vanessa*, *Dytiscus*, have a monophasic retinal potential, cornea negative, are very sensitive to state of light adaptation, have high absolute sensitivity, have fusion frequencies of the retinogram of 40 to 60 per sec., and optic ganglion spontaneity at 20 to 30 waves per sec.; these are often night-flying insects. In a second group, illustrated by *Calliphora*, *Apis*, *Vespa*, *Eristalis*, *Bombus*, the electroretinogram is diphasic with the cornea initially positive and with on and off responses, less dependence on adaptation and lower absolute sensitivity, fusion frequencies 160 to 300 per sec., optic ganglion spontaneity at 120 to 160 per sec.; these are day insects which discriminate fast-moving objects in bright light. Removal of the optic ganglion from type II converts the retinogram to that of type I, and in *Aeschna* the larva is similar to type I but as the ganglion approaches the retina the adult becomes type II.

The *Limulus* eye is of Autrum's type I. This eye continues to yield interesting results (75); records obtained from single ommatidia show a slow "retinal" potential with nerve spikes superposed, from which of several cells is not certain. The retinal potential is conducted electrotonically and may excite the nerve, since similar cathodal polarization elicits a volley of nerve impulses. An unexpected observation is that a single unit can be inhibited by stimulation of adjacent ommatidia, hence the concept that there is no peripheral interaction in the *Limulus* eye is incorrect. An amplifier of short

time-constant revealed two components in the gross electroretinogram of *Limulus*, one possibly from the eccentric cells and the other possibly from radial cells (76). Simple electroretinograms were recorded from the eyespot of a starfish (75) and from the ocelli of *Limulus* (77).

Microelectrodes have been used in several investigations on vertebrate retinas. In the frog, evidence was obtained that the rods give a positive and the cones a negative deflection in the electroretinogram (78). The component P III appears to come from rods (79, 80). Microelectrode records from single ganglion cells and their fibers in cat and rabbit retinas are showing the complex integrating properties of the retina, variable response patterns and latencies, spontaneous activity, inhibition, and other characteristics of nerve centers (81 to 84).

Observations of behavior have added significantly to knowledge of visual function. Optomotor reactions are specific responses to movement of a striped field, either flat or cylindrical (3). In a stationary field a moving insect can respond to the shift in retinal image produced by its own movement (85). Fusion frequencies measured by optomotor responses agree well with those by electroretinograms for insects with fast and slow eyes (86). Fast-moving species of animals tend to have high fusion frequencies of vision (87). In a series of 27 species of Hymenoptera (apposition eyes) it appears that the number of ommatidia is adjusted so that the interommatidial angle is just below the resolving power of an ommatidium (88). Detection of motion, however, requires central evaluation of stimulation of adjacent ommatidia (89), and impulses in the central nervous system of *Locusta* show detection of a light-dark boundary until the angular movement is reduced to  $1^\circ$  which is close to the angular separation of ommatidia (90). *Apis* fixates only with the central part of its eye (91).

Evidence is accumulating from a variety of animals for true color vision, although it is not always distinguished clearly from differential spectral sensitivity (87). In *Drosophila*, the optimal color shifts toward shorter wave-lengths with decreasing intensity, a Purkinje shift which is indicative of two receptor types (92, 93), although it is difficult to obtain a true action spectrum because of the presence of filter pigments (94). Electroretinograms of *Calliphora* show a very wide spectral range, peak sensitivities at 540 and 630  $m\mu$ ; by matching with neutral grays evidence was obtained for true color vision based on two types of receptor (95). Experiments indicating that bees can distinguish four colors, yellow, blue-green, blue and ultraviolet, have been summarized (96). Optomotor reactions suggest that some butterflies have separate receptors for orange-red, yellow, and green-blue (97). The octopus has color vision (98). A series of microcrustaceans, especially *Daphnia*, are photopositive to longer wave lengths (yellow) and photonegative to shorter ones (blue); at low temperature they are positive to all colors, a phenomenon which may be important in diurnal vertical migrations (99). Color vision (blue, green, and red) is indicated for the giant tortoise (100).

and the carp (101), but amphibians vary much according to species (102, 103, 104).

Epidermal photoreceptors connected to the lateral line occur in lamprey larvae (105, 106), and the dorsal integument is photosensitive in aquatic larvae of some beetles (107). The function of the pineal as a photoreceptor in many teleosts varies with the amount of covering pigment (108).

The light compass reaction of arthropods was explained by the discovery that bees can distinguish the plane of vibration of polarized light and that they communicate direction to other bees by a characteristic dance in the hive, transferring the visual cue to gravity on a vertical comb in the dark or running in the proper direction on a horizontal comb if they can see a bit of blue sky. The bee is disoriented in its horizontal dance if the plane of polarization of visible light is changed by rotating polaroid, but the bee can correct for changes corresponding to lapse of time (109, 110). In the field, bees orient themselves by objects in the landscape, by the position of the sun and by plane of polarization of light reflected from the sky (111). Ability to distinguish plane of polarization has now been found in ants (112), *Drosophila* (113), in some hymenopteran and lepidopteran larvae (114), in *Limulus* (115, 116), in the hermit crab *Eupagurus* (117), and in Cladocera (118). Detection of plane of polarization has been ascribed to a birefringent filter (probably crystalline cone) and subsequent retention of only one beam (116, 119, 120). It has also been explained on the basis of Fresnel's law, namely difference in reflection of light in different planes of vibration, hence sharp intensity differences at the reticular cells (113, 118). Comparative studies on visual pigments were recently listed in this publication (121).

#### CHEMORECEPTORS

There is still no unifying theory for chemical senses. Blowflies extend the proboscis when the tarsus touches a solution of an attractant such as sugar and withdraw the proboscis in response to a repellent such as alcohol on a tarsus, probably by two different kinds of receptors (122). Tests with some 200 aliphatic hydrocarbons rejected by *Phormia* showed no sharp correlation with chain length or boiling point, although threshold concentrations rose with increasing water solubility, and effectiveness was decreased by branching of a chain (123). The shape of the curve relating effective concentration to carbon chain length varies with solvent (124, 125), and breaks are often found; possibly stimulation can be by either aqueous or lipid phases; there were similar breaks in threshold curves for an aquatic beetle (126). Taste thresholds of blowfly tarsi for glycols and alcohols decrease more sharply with increasing chain length than for human taste (125). Stimulation by mixtures of glycol and fructose results in adaptation to each, partly central and partly peripheral (127). Similar proboscis responses occur to olfactory stimulation of receptors on antennae and palpalae (128). Here better correlation between threshold and thermodynamic activity of different compounds is found (129).

Field-type tests on sugar preferences and the effects of repellents have

been made (130, 131). Natural odors are important in the discovery of food by bees (132), and cabbage butterflies (133), in location of members of the opposite sex in Lepidoptera (134), and in recognition of hive-mates in bees (135). The infrared hypothesis of olfactory stimulation was contraindicated (136).

A promising hypothesis for homing behavior in fish is based on their discrimination and memory of specific chemicals. Bluntnose minnows showed, in training experiments, the ability to detect *p*-chlorophenol at concentrations of at most 0.0005 p.p.m. and to distinguish this from *o*-chlorophenol (137). The fish were then trained to discriminate dilute rinses from aquatic plants, to recognize water from different feeder streams by their organic components (137, 138). These ideas are being tested with respect to home stream recognition in salmon. High chemosensitivity was demonstrated for earthworms (139), lizards (140), and quail (141).

Reviews of the morphology and physiology of olfactory systems in vertebrates, particularly mammals, appeared (142, 143). In the olfactory bulbs of the rabbit different fiber groups are active in response to slightly different odors (144). Electrical records from taste fibers indicated that dogs but not cats have a sweet taste (145), but conditioning experiments showed that cats can taste sugar (146), probably by other nerves than those used for electrical recording. No progress seems to have been made in recording impulses from chemoreceptor nerves in any invertebrate or fish although preliminary results are reported for *Limulus* (147).

Receptors sensitive to CO<sub>2</sub> or to O<sub>2</sub> lack are known for many animals, some of them internal as in mammals and some external as in certain aquatic animals. In *Limulus*, external receptors sensitive to CO<sub>2</sub>, to high and to low O<sub>2</sub> were demonstrated as present, but were not located (148). In *Aedes*, CO<sub>2</sub> receptors were localized to the first flabellar segments of the antennae (149).

In exploring the tongue of the frog for taste endings, specific water receptors were discovered (150, 151, 152). It is suggested that these may function reflexly to keep the mouth closed. Hygroreceptors were clearly localized in regions of the antennae of *Aedes aegypti* and of *Blatella* (153) and of *Tribolium* adults (154, 155, 156), also in specific sensillae on beetle larvae (156). The antennal hygroreceptors are directional, and the *Tribolium* adults normally show a preference for lower humidity over the range of 30 per cent to 100 per cent R.H. and can distinguish differences of 5 per cent R.H. in certain ranges, but on desiccation the response reverses to preferences for higher humidity (154). *Drosophila* select 77 per cent R.H. at 20°C. in preference to higher or lower values but when desiccated they select higher humidities (157). Numerous terrestrial animals show humidity preferences: beetles (158), mites (159), and *Peripatopsis* (160).

#### THERMORECEPTORS

In a series of papers on thermoreception in mammals Hensel & Zotterman (161 to 168) have shown that absolute temperature of skin thermoreceptors



is more important than spatial temperature gradient across the skin. Single fibers from either cold or warmth receptors are spontaneously active, cold endings being least active at body temperature, activity increasing on cooling (maximum at 25 to 35°C.) and paradoxically at very high temperatures, while warmth endings show maximum activity above body temperature (38 to 43°C.). Spontaneous activity was also observed from thermoreceptor endings in the pits of rattlesnakes, spontaneous activity being modulated by radiant heat corresponding to a temperature rise in the pit membrane calculated at a few thousandths of a degree (169, 170), contraindicating the hypothesis that the pit is a pneumatic heat detector (171).

Specific thermoreceptor areas were located in paired crescents and fenestrae on the head, thorax, and abdomen of *Locusta* (172) and in distal segments of the antennae of some beetles (173). Temperature selections in an ecological gradient need not necessarily involve specific thermoreceptors. Preferred temperatures were demonstrated for bees (174, 175).

#### MECHANORECEPTORS

*Low frequency receptors.*—These include touch and stretch receptors of many types; proprioceptors were classified by Lissmann (176). When muscle spindles are stretched, a local potential is generated at the ending, comparable functionally to retinal and cochlear potentials (177); also in Pacinian corpuscles local responses are found (178, 179). Sensory adaptation was followed in Pacinian corpuscles (180, 181), in touch receptors in frog skin (182), in baroreceptors of the carotid sinus (183), and sensory adaptation was shown to differ from axon accommodation (181). The reflex significance of muscle spindles, regulated by small motor nerve fibers to intrafusal muscle fibers, and of tendon receptors has been elucidated (184, 185).

A new type of muscle receptor, analogous to mammalian spindles, was found to occur in pairs in thoracic and abdominal segments of *Homarus* and *Palinurus* (186, 187, 188). Each unit consists of a thread-like muscle ramified in one region by dendrites of a large peripheral sensory neurone; the muscle element has motor innervation plus two accessory motor fibers which ramify in the sensory neuropile. Similar receptors occur in *Cambarus*, two pairs dorsally per segment; one of each pair has a lower threshold of stretch and is nonadapting; the other has a high stretch threshold and is rapidly adapting (189).

Quantitative analysis of the responses from sensory spines of the femur of a cockroach shows that the frequency of response leads a sinusoidal mechanical stimulus; the significance of this response, nonlinear with respect to intensity, is considered in terms of control system theory (190). Multiple functions are indicated for abdominal mechanoreceptors of *Dytiscus* which respond at breathing movement, also to vibrations of 100/sec., occasionally at 1400/sec. (191).

The relation of mechanoreceptors to animal distribution has not been

much considered, but there must be correlations with bottom and stream velocity selection. Of two related species of crayfish, one is a mud-dweller and the other prefers a stony bottom (192). The positive rheotactic speed of planaria increases to a maximum at a critical rate of flow (193). The fry of chum and pink salmon move toward fast water while fry of coho salmon aggregate in deep quieter water (194).

*Lateral line receptors.*—Lateral line receptors are intermediate in a functional classification between tactile receptors and true sound receptors, and their function has been called "distant touch sense" (195). The hair cells vary in degree of exposure and protection, and in aggregation into organs (195, 196). In the ruff *Acerina* recording very close to the cupula gives an electrical wave comparable to the microphonic of the ear. In the range 14 to 48 c.p.s. the electrical output is proportional to the amplitude of movement of the cupula over the hair cells; the cupula compares functionally with the tectorial membrane (197).

All lateral line nerves examined show much "spontaneous" activity, and this is not necessarily related to fluid movement in the canal. Single fiber records from a Japanese eel show irregular impulses (198). The sense cells in the eel are grouped in organs which receive two types of nerve fiber, thick ones centrally and thin ones peripherally (199). Stimulation is mechanical and best by a stream of water; at low frequencies there may be several impulses per mechanical wave, at about 20 to 50 c.p.s. for one impulse, and at higher frequencies some spikes drop out; the thick fibers follow at higher frequencies (100 c.p.s.) than the thin fibers (200, 201). In *Fundulus* at a water pressure of 20 dynes/cm. the gross discharge of the nerve follows vibrations to at least 180 c.p.s. (202).

*Auditory function of the ear.*—It has been argued that hearing antedated gravity sense in vertebrates, possibly also in crustaceans and some other invertebrates (203). Important recent developments in cochlear physiology are: (a) the discovery of a D.C. potential of 100 mv. across the organ of Corti, i.e., between the scala vestibuli and scala media (204), (b) the discovery by microelectrode recording from single auditory fibers that many of them show spontaneous activity and that the fibers from the basal turn respond at all audible frequencies, not merely at high frequencies (205), and (c) the hypothesis that the cochlear potential results from a change in resistance at the basilar membrane permitting current to flow and that this may excite the basket of nerve endings around the hair cells (206). It is interesting that the lateral line shows both the spontaneous activity and microphonic potential.

The vertebrate ear has developed from the lateral line system to vestibular and ultimately cochlear mechanisms. In fishes the semicircular canals sense angular acceleration, the utricle has static-dynamic function, the saccule and lagena (pars inferior) and in some fish also the utricle, an acoustic function; this sequence was reviewed by Dijkgraaf (207, 208).

Hearing tests (by behavior) in a variety of fish show high sensitivity in the lower frequency range, nearly constant sensitivity from about 60 to about 1000 c.p.s., then a sharp rise in threshold (195, 209, 210). Minnows distinguish tone intervals of thirds and fifths well, not octaves (211). Fish in which the swimbladder is coupled by the Weberian ossicles to the pars inferior of the ear can hear at higher frequencies and with lower threshold and can discriminate tones better than when the Weberian ossicles are missing or have been removed. There are marked species differences, the minnow *Phoxinus* being less dependent on the Weberian ossicles than the catfish (208, 209, 212, 213).

In contrast to fish which hear better than man at low and less well at intermediate frequencies, birds such as pigeons and songbirds hear very poorly if at all below about 1000 c.p.s. but appear to hear well up to about 25,000 c.p.s. (214, 215, 216). A number of rodents give reflex responses to high frequencies, deer mice in the range of 10 to 65 kc. (217), bank voles and dormice to about 50 kc. (218, 219).

Sound production is widespread among insects, and sensitivity of insect phonoreceptors is often very high. Action potentials in leg nerves from various sound receptors show a wide range of frequency sensitivity (227). Locusts produce a variety of distinguishable patterns of sound, each with its peculiar behavioral significance (203, 228).

*Echolocation and related function.*—Response to high frequency sound is often associated with echolocation, described in detail for bats (220, 221, 222). The best-known bats (Vespertilionidae, particularly the brown bat *Myotis*) emit sound pulses of 2 to 5 msec. duration in the laboratory, longer in the field, each pulse starting at about 80 kc. and declining to about 40 kc., the clicks being repeated some 20 to 30 times per second; the bats can hear sounds of even higher frequencies. The Rhinolophidae emit clicks of pure tones (80 to 100 kc.) in 100 msec. pulses and forwardly directed (223). Flying bats use the reflected sound in locating food insects and in avoiding obstacles. Echolocation is also suspected in various rodents which emit sounds up to 30 kc. (224), and in porpoises which respond to sounds up to 30 kc. (225). Underwater sound is produced by many fish, usually by means of the swimbladder (213) and echolocation, although not proved, is quite possible in fish.

The water beetle *Gyrinus* appears to use specific antennal mechanoreceptors to detect reflected or disturbed water waves and thus to avoid obstacles (226).

A different sort of signalling is indicated for some electric fish which give off a continuous discharge of electrical pulses and which appear sensitive to changes produced by objects in the surrounding electric field (229). What sensory structures detect such small electrical differences is unknown.

*Hydrostatic pressure sense.*—The swimbladder functions by changes in gas volume to regulate the density and hence the level in water of fish, and there have been suggestions of hydrostatic pressure receptors in the wall of

the swimbladder. However recent evidence suggests that the pressure receptors are not in the swimbladder (213, 230) but more probably in the pectoral fins (231). In the vertical migration of microcrustaceans, particularly larvae in plankton, there is evidence that an unidentified pressure sense is important (232). An aquatic bug, *Aphelocheirus*, which has plastron respiration and remains submerged, possesses a pair of specialized sensilla which are stimulated when changes in hydrostatic pressure move the respiratory bubble (232a).

#### EQUILIBRIUM SENSE

The pars inferior is usually considered as the phonoreceptor portion of the fish ear. However, in clupeids the acoustic function may be in the utriculus, and in a ray the vibration sense resides in both utriculus and sacculus; vestibular microphonics follow up to 750 c.p.s. (233, 234). In birds in which the cochlea has been destroyed, microphonic potentials are recorded from the bony walls of the ampullae of the semicircular canals at sound frequencies up to 100 to 300 c.p.s. (235, 236). It is thus evident that the vestibular portion of some ears can perceive sound.

The equilibrium sensory function of the labyrinth has been examined in a series of papers (see 237). Oscillographic records from single fibers of vestibular nerves of the ray, *Raja*, show a constant background of spontaneous activity. Rotation in ipsilateral direction increases the discharge, and rotation contralaterally decreases the discharge from a given canal, maximum response is to acceleration in the plane of the canal. When the cupula-endolymph is considered as a damped torsion pendulum, such that  $\pi/\theta = 4\eta/\sigma r^2$  where  $\pi$ =damping factor,  $\theta$ =moment of inertia,  $\eta$ =viscosity,  $\sigma$ =density, and  $r$ =radius, the agreement between measured frequency of nerve impulses and angular rotation and the calculated values is good (238). Similar theory has been applied more indirectly to mammals (239), and impulses have been recorded from mammalian vestibular nerves under centrifugal stimulation (240).

When recording is from a nerve twig from utriculus, sacculus, or lagena of the ray, two types of response to stationary position are noted, one for side up and nose up, the other for side up and nose down; all three otolith organs participate in the equilibrium sense (233, 241). It is evident that a given region of the ear of the ray may contain receptors sensitive to acceleration, to position relative to gravity, and to vibration (237).

Behavioral responses of fish to gravity were interpreted as indicating stimulation of a macula when a statolith is on the side, not at the top or bottom relative to the stimulated hair cells (242). When the utriculus is removed unilaterally there is good central compensation for the asymmetry (243). Similar compensation occurs in frogs (244). The three pairs of otoliths were made visible in fish (245). There is emerging a unified picture of the functioning of the lateralis-vestibulo-acoustic system, all parts of which de-

pend on hair cells as intermediate between mechanical pressure waves and nerve excitation, and all parts showing responses which are modulation of spontaneous activity.

The statocysts of invertebrates are equilibrium receptors which lack true hair cells. Recent observations on crustacean statocysts show spontaneous activity in some of the fibers of the statocyst nerve, effective stimulation by angular motion, less effective by static stimulation, and least by sound (246). The mechanoreceptors at the base of dipteran halteres are functionally analogous to the horizontal canals of vertebrates (237). Evidence that the halteres serve as gyrocompasses is summarized (247). In locusts five patches of sensory hairs on the head are so stimulated by wind currents that the insect tends to maintain a position of equal stimulation on both sides, stabilization of yaw (248). In the dragonfly, *Anax*, sensillae on the neck region determine the position of head relative to thorax (249).

#### DIRECTION SENSE IN BIRDS

One of the most puzzling topics in comparative physiology is the sensory basis for homing and migration in birds. Most of the current literature is behavioral and merely the nature of the problem can be indicated here; current theories are summarized by Griffin (222, 250). The theory of magnetic sense seems disproved on the basis of the absence of magnetically sensitive material in a bird and on the lack of effect of magnets attached to homing pigeons (251). Sensitivity to coriolis forces is unlikely by virtue of their negligible magnitude relative to atmospheric disturbances and their other physical requirements; however, an inflatable membrane over the eardrum was interpreted as a possible shield against wind (252). Orientation with respect to the sun is certainly used in some instances as indicated by disorientation of homing pigeons on cloudy days (253); however, birds do not appear able to distinguish plane of polarization of light (254).

By following individual released birds, mostly of wild species, evidence for systematic search for familiar landmarks was obtained (250). Statistical analysis of flight data, however, led to the conclusion that random search might account for return of wild birds to home territory (255). Trained birds may fly in habitual, trained direction even over unfamiliar territory (250, 253). Also migrating birds often take the familiar direction even when transported great distances east or west from normal migration routes [Mayr (250)]. Birds trained to a given direction correct for lapse of time and may well share with many other animals an innate time sense or rhythm (256). The sensory cues used as compass in night orientation and in direct homing over strange territory remain unknown.

#### CONCLUSIONS

Some generalizations can be drawn from the papers summarized in this review. Nerve nets, considered as primitive diffuse nervous systems, are far

from simple and possess many of the properties of centralized nervous systems such as facilitation, spontaneity, functional differences in different tracts. Use of electrical recording in nerve nets is promising.

A sufficient number of single synapses of giant fiber systems has now been analyzed with respect to polarization, facilitation, fatigue, effects of drugs, and maximum frequency of transmission to provide a series of types. It seems certain that no single hypothesis can describe transmission in all giant fiber junctions. Small-fiber systems and interaction in a neuropile are not yet amenable to unitary analysis; in these we may expect still different properties from those of giant fiber synapses, properties of field effects. The analysis of simple memory function in the brain of the octopus provides a concrete example for application of communication theory to learning, a trend which is likely to increase in the next few years.

The discovery of new nervous structures and sense organs by Alexandrowicz shows the need for more comparative histology.

The compound eye of arthropods, even devoid of optic ganglion, is not so simple as had been supposed, and the use of microelectrode techniques may be expected to elucidate the functions of the different reticular cells and to help explain color vision and discrimination of plane of polarization which have been demonstrated in behavior. Chemoreception remains the most elusive of all senses as to mechanism, and further there have been discovered external  $\text{CO}_2$  and  $\text{O}_2$  receptors and specific water receptors.

The discovery of special muscle fibers associated with stretch receptors in crustaceans suggests that the principle of the muscle spindle may be widespread. The functional continuity and even multiplicity of function among lateral line organs, semicircular canals, otolith organs (utricle, saccule, and lagena), and cochlea indicate a remarkably close evolutionary series.

An increasing number of sense organs has been shown to produce graded local potentials which, spreading electrotonically, may serve to excite nerve endings, as in retinae of both compound and simple eyes, cochlea, lateral line organs, muscle spindles, and Pacinian corpuscles. Spontaneous activity has been demonstrated from sensory endings of an increasing number of nerves (thermoreceptors, auditory, lateral line, vestibular nerve fibers) and from ganglion cells in receptors (optic ganglia); sensory stimulation must be viewed in these instances as modulation rather than initiation of activity. There is still no concrete evidence correlating structure of sensory endings with function (257). Thermoreceptors and mechanoreceptors seem to act similarly whether encapsulated or free endings.

Still more sensory mechanisms are indicated but not yet identified, such as external  $\text{CO}_2$  and  $\text{O}_2$  receptors, electric field detectors, organs of hydrostatic pressure sense, receptors used in directional flight by birds. Sensory function has been very little correlated with animal distribution and with the very important diurnal, tidal, and seasonal rhythms which seem to be inherent in many animals, possibly in their nervous systems.

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## ENERGY METABOLISM

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The present review covers the more important articles published in the interval between the review of Chambers & Summerson in 1950 (1) and May 1953 with special emphasis on the last two years. The term energy metabolism is a broad one but for the purposes of this volume has been limited to the regions explored by Rubner and Lusk. Energy metabolism at the cellular level is not covered. The effects of heat and cold are treated in another chapter, but it has seemed advisable to include a few references which show how they influence heat production.

### BASAL METABOLISM STANDARDS

For many years it has been obvious that the older standards (2, 3) were set at levels which were too high. This was due to the fact that they were based partly on first tests with untrained subjects. There have been many estimates as to the effects of training when tests are repeated on several days. Vogelius (4), studying girls, found the level decreased an average of 8 per cent, Rodahl (5), with Eskimos, 9 per cent. Robertson & Reid (6) have gone to the extreme of securing the lowest readings. They studied their normal controls at least 12 hr. after a very small evening meal and made their tests on successive days until no further fall in heat output was observed. Then "the lowest reading observed in the series was taken as an estimate of the true basal level of metabolism." This selection of the lowest instead of the average of several technically acceptable readings has been criticized.

Fleisch (7) has recently worked out a set of new standards in an excellent manner. First he tabulated the figures for kcal. per m.<sup>2</sup> per hr. taken from 24 sets of standards. Next he found the arithmetic means for each age and then modified these according to the number of subjects and his estimate of reliability. Finally he smoothed the curve and gave the figures shown in Table I. A synthesis of less satisfactory nature has been made by Quenouille *et al.* (8). They have assembled from all available reports 8600 subjects, but it does not look as if their selection were based on much personal experience with basal metabolism. Their regression formulas make it difficult to compare their standards with those of other authors.

In Table I are given the new standards of Fleisch (7) and of Robertson & Reid (6) as compared with the older ones of Boothby, Berkson & Dunn (3) [Mayo] and of Lewis, Duval & Iliff (9) [Child Research Council]. Fleisch's lines for boys and girls are close to those of Lewis, Duval & Iliff and distinctly lower than the two others. For adults they are between them. The advantage of using surface area as a reference point for man has been discussed by Fleisch (7). Keys (10) in one report says that the Boothby (Mayo)



TABLE I  
NEWER STANDARDS OF BASAL METABOLISM†  
kcal. per square meter per hour

Age—Years	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
<i>BOYS</i>																
Fleisch	53.0	52.4	51.3	50.3	49.3	48.3	47.3	46.3	45.2	44.0	43.0	42.5	42.3	42.1	41.8	41.4
Rob.	—	—	60.1*	57.9	56.3	54.2	52.1	50.1	48.2	46.6	45.1	43.8	42.7	41.8	41.0	40.3
B. B. & D.	—	—	—	—	—	53.0	52.4	51.5	49.9	48.0	47.2	46.8	46.5	46.4	46.1	45.5
Lewis	—	56.9	54.5	52.6	51.0	49.6	48.2	46.6	45.0	43.6	42.2	41.5	41.4	41.1	40.5	—
<i>GIRLS</i>																
Fleisch	53.0	52.4	51.2	49.8	48.4	47.0	45.4	43.8	42.8	42.5	42.0	41.3	40.3	39.2	37.9	36.9
Rob.	—	—	54.5*	53.9	53.0	51.8	50.2	48.4	46.4	44.3	42.4	40.6	39.1	37.8	36.8	36.0
B. B. & D.	—	—	—	—	—	50.5	48.5	46.7	46.1	45.7	45.1	43.9	42.5	41.1	39.7	38.6
Lewis	—	52.9	51.3	49.9	48.4	46.9	45.5	44.0	42.7	41.4	40.4	39.7	38.4	36.8	35.2	—
Age—Years	17	18	19	20	25	30	35	40	45	50	55	60	65	70	75	80
<i>MEN</i>																
Fleisch	40.8	40.0	39.2	38.6	37.5	36.8	36.5	36.3	36.2	35.8	35.4	34.9	34.4	33.8	33.2	33.0
Rob.	39.7	39.2	38.8	38.4	37.1	36.4	35.9	35.5	34.1	33.8	33.4	33.1	32.7	32.4*	32.0*	—
B. B. & D.	44.4	42.9	42.2	41.6	40.3	39.6	38.9	38.3	37.6	37.0	36.3	35.7	35.1*	34.5*	33.4*	—
<i>WOMEN</i>																
Fleisch	36.3	35.9	35.5	35.3	35.2	35.1	35.0	34.9	34.5	33.9	33.3	32.7	32.2	31.7	31.3	30.9
Rob.	35.3	34.9	34.5	34.3	34.0	34.1	33.5	32.6	32.2	31.9	31.6	31.3	31.0	30.7	—	—
B. B. & D.	37.6	37.0	36.6	36.3	36.0	35.8	35.7	35.5	35.3	34.4	33.4	32.8	32.4*	32.2*	32.0*	—

\* Extrapolated or based on less than 7 subjects.

† The new standards of Fleisch (7) and of Robertson & Reid (6) compared with the older standards of Boothby, Berkson & Dunn (3) [Mayo Clinic], and of Lewis, Duval & Iliff (9) [Child Research Council].

standards are about 10 per cent too high, in another paper (11) he quotes the results on 34 normal subjects whose average was  $-11.8$  per cent. Fleisch estimates his average 8.5 per cent below the Mayo standards.

It is difficult to give advice regarding the adoption of new "clinical standards." For many years clinicians have been in the habit of thinking in terms of percentage deviation from the old standards of Aub & Du Bois (2) (Sage) or of Boothby, Berkson & Dunn (3) which are better because they are a little lower. Experienced clinicians discount high results on the first test and make allowance for the high level of the standards. Probably most clinics will keep on using these standards because a change would upset the continuity between old and new determinations.

It is a different matter when we come to "physiological standards" needed for careful research on race, climate, and other factors. If a study is made using the special technique of Robertson & Reid (6) their standards for British adults may well be applied. It is not clear why their figures for children are so high. On the whole, the standards of Fleisch (7) appear to be the best for general use, the "most physiological."

The profound effects of starvation and rehabilitation have been covered in authoritative manner by Keys and co-workers (11). They also followed changes in body composition. A large number of obese children were studied in Denver (12, 13) and at The New York Hospital. Only 3 per cent of them were lower than  $-15$  per cent of the Child Research Council standards according to surface area. Small, large, thin, short, and tall children showed similar moderate deviations, and the authors believe that their standards can be employed for children of unusual build except in the cases of dwarfs and very small children.

Rodahl (5) in an important study of Eskimos has explained the apparently high metabolic rates reported by previous observers. He made 340 determinations on 52 male and 21 female Eskimos in four native villages and used 28 whites as controls. The results on the first day averaged 9 per cent higher than on the third day, but the levels remained higher than the white standards. Even after the usual night's fast some of them were excreting 3 gm. of nitrogen per hr., about six times the average level for medical students in the United States. Fourteen Eskimos studied in the field averaged 8 per cent above the white standards of B.M.R. When the Eskimos were brought to the Arctic Aeromedical Laboratory and kept for three or more days on white man's diet, the urinary nitrogen dropped to 0.4 gm. per hr. and the average B.M.R. fell to  $-8$  per cent, the same as the average of 16 white men under similar conditions. Rodahl concluded that there was no racial difference. Probably many differences which have been ascribed to race or climate are due to other factors.

Quiring (14) has found that West Indian and New Orleans negroes fall within the range regarded as normal for the white population. Galvão (15) in Brazil has continued his important investigations of basal metabolism in the tropics. His results on 48 females tend to support his contention that al-

though B.M.R. in North America is proportional to surface area it is better represented by "metabolically active weight" in the tropics. He did not find any change with age between the years of 12 and 48 according to his formulas but observed surprisingly high rates (average +29.6 per cent) of the sexually immature girls between the ages of 12 and 15. This prepubertal elevation is much greater than in studies from North America and Europe. Some have denied that puberty has any significant effect but almost all curves, unless greatly smoothed, have shown a decline in the rate of fall of metabolism or even a plateau just before puberty in boys and girls (7, 16).

#### BODY COMPOSITION AND THE SURFACE AREA LAW

"Metabolically active weight" is a vague term similar to "protoplasmic mass," but there have been attempts to measure it. Behnke, Feen & Welham (17) developed the method of estimating the fat content of a man by immersing him in water and determining the specific gravity. Figures below 1.060 indicated obesity. They showed that the overweight tables could be deceptive in the case of athletes. Behnke, Osserman & Welham (18, 19) measuring total weight and specific gravity can estimate the Lean Body Mass (L.B.M.) which they find contains about 72 per cent water, 19 per cent protein, 7 per cent minerals, and 2 per cent essential lipid material. Keys, Anderson & Brožek (20) and Brožek & Keys (21, 22) in a series of studies have reported specific gravities of many individuals and have compared the results with other methods of estimating fatness. In their analysis of 273 healthy men of the white collar class they found the average fat percentage of the body at the age of 20 was 10 per cent and that it increased steadily until it reached 25 per cent at the age of 55. Taylor, Brožek & Keys (23) determined basal cardiac outputs in 34 healthy male students and found a correlation coefficient ( $r$ ) of 0.54 to body weight, 0.60 to surface area, 0.74 to the weight of the lean body mass, and only 0.16 to the weight of fat. Miller & Blyth (24, 25) also have used the Behnke method on college students and have noted that they could predict the lean body mass quite well, either from the basal oxygen consumption or from the creatinine excretion. Reports on body water have been made by several laboratories (26, 27, 28).

Vogelius (4) has reviewed the various methods of measuring the surface area of humans and has concluded that the old "Height-Weight Formula" of Du Bois & Du Bois (29) gives a close enough approximation. He finds that their "Linear Formula" gives figures on the average 2.3 per cent lower with girls but is probably better for people of unusual form. Rodahl (30, 31), studying Eskimos, found the "Linear" on the average 0.9 per cent lower than the "Height-Weight." Guibert & Taylor (32) have made additional studies on the radiation areas of men in different positions since for all determinations of heat loss it is this profile area that counts. Using the "Height-Weight Formula" as a basis of 1.00 the average relationships were: erect, 0.77; semi-erect, 0.72; seated, 0.70; crouched, 0.65; light clothing, 1.14.

The big question as to the significance of body size and surface area in

relation to metabolism in the animal kingdom is still under lively discussion. Perhaps the most important work is that of Zeuthen (33, 34). In his 1947 paper he finds that animals weighing less than one gram most frequently do not obey the surface law and that "the metabolic intensity of the animals decreases most markedly with increasing body size in the range of medium sized animals, however gradually less for smaller, maybe, also for larger animals." He believes that the relative decrease of surface with size has nothing to do with heat regulation, which, from an evolutionary standpoint, is of very recent date. His 1953 paper is an important and stimulating discussion. Here he tabulates data from the bacteria and protozoa up to small mammals. The fact that poikilothermic animals show levels of metabolism proportional to surface has always puzzled those who lean towards a causal relationship between surface area and basal heat production. This has led to a search for other relationships between body size, vital organs, and functions. Kayser (35) leans towards the older theories of Lambert & Tessier (36). Bertalanffy *et al.* (37, 38, 39) describe three metabolic types: (a) proportional to the  $2/3$  power of weight, (b) to weight, (c) intermediate. Adolph (40) refers 34 bodily functions or sizes of organs to various exponents of body weight. Mitchell (41) in a most interesting article lists nutrient requirements in proportion to body weight, surface area, or  $Wt^{0.75}$ , and those which are proportional to total heat production.

#### ENDOCRINES

The integrative action of the endocrine system is well reviewed by Means (42). With Lerman & Harington (43) he has studied the physiologic activity of some of the analogues of thyroxine. Skanse (44) working in his clinic has made an extensive review of tests of thyroid activity. He says, "The B.M.R. may be considered to be an index of the impact of thyroid hormone on the body cells. The serum protein-bound iodine is an index of the hormone level proper. The excretion of  $I^{131}$  reflects the gland's avidity for iodine." The B.M.R. is unreliable in borderline and atypical cases. Important discussions of these same points have been published by many authors (45, 46, 47).

Derrick & Collip (48) have reported on the metabolic effects of a new pituitary factor. Ryer & Murlin (49) add to our knowledge of the actions of thyroid hormones and insulin on metabolism. Kuhl & Ziff (50) report that adrenocorticotropin and cortisone caused no significant change in B.M.R. in their ten patients. Mayer and others (51) describe the very low B.M.R. of hereditarily obese mice. Bauer & Lembeck (52) discuss the effects of nor-epinephrine, and Griffith (53) gives a detailed review of the calorogenic action of epinephrine.

Kayser (54 to 57) has continued his exhaustive studies of hibernation. Hock (58, 59), working with bats, has followed their marked fluctuations in body temperature and metabolism, and Pearson (60) in a popular article on humming birds has demonstrated their low metabolism during the night time.

## COLD AND HEAT

The effects of cold and heat are treated in detail in another chapter. The old question as to whether or not there is a "chemical regulation" in man has been partially clarified. Wezler & Neuroth (61), continuing the work of Thauer, studied four men and two women in a climatic chamber at different temperatures. They found great variability in the rise of metabolism in the cold, and they bring out the important point that when the peripheral zone of the body cools and has a low metabolism the core of the body must compensate by a considerable increase. Du Bois, Ebaugh & Hardy (62) in a detailed study of 13 women in the Sage calorimeter report on the various channels of heat loss at different temperatures. They find that some women in the cold zone show a small increase in metabolism without evidence of increased muscle activity. Krag & Kountz (63, 64) compared the effects of heat and cold on old and young subjects.

There does not seem to be any significant change of B.M.R. in men acclimated to cold (65). Brody and his associates (*see* 66) have continued their classical studies on domestic animals. Scholander *et al.* (67) give a fascinating account of the effects of cold on small animals in Alaska. Mitchell & Edman (68) review nutrition and climatic stress.

## WORK

Göpfert, Eiff and their co-workers (69 to 73) have made extensive studies of metabolism comparing it with a sensitive method of recording muscle action currents. Abbott & Bigland (74, 75) report on the physiological cost of negative work, and Bahnson, Horvath & Comroe (76) show the increase in oxygen consumption with passive movements of the limbs. Physical fitness and the detailed responses of work and recovery have been examined by Bruce and others (77), and by Henry & De Moor (78) and Henry (79). Various other aspects of work have been covered in several laboratories (80 to 84).

## TECHNIQUE

Benzinger & Kitzinger (85) have described their important gradient calorimeter with very rapid response, and Prouty & Lawton (86) have applied it to small animals. Erikson, Scholander & Irving (87) improved their large respiration apparatus which makes many simultaneous recordings, and Scholander *et al.* (88) report an ingenious microrespirometer. Fleisch (89, 90) has developed a new ergostat and a double spirometer. Richards, Stoll & Hardy (91, 92) are devising new apparatus for measuring radiation. White, Lundgren & Boothby (93) show a small error from nitrogen in closed circuit machines, and Willard & Wolf (94) bring out emphatically the errors caused by changes in type of respiration. Finally Bruger & Hollander (95) manage to list 42 factors, diseases or technical errors, that can give the picture of hypermetabolism.

## SPECIFIC DYNAMIC ACTION

In this field there are the greatest possibilities for errors. Swift (96), continuing the work of Forbes, has made an excellent review. He says,

Any studies of dynamic effects of food must provide that the planes of nutrition involved be at or above that of energy equilibrium. The dynamic effect of a single nutrient, determined directly, bears no significant relation to the dynamic effect of diets of which the nutrient becomes a part.

In some countries practitioners have postulated a correlation between low specific dynamic action and pituitary disease. One suspects that it is a correlation between faulty technique and even faultier diagnosis.

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## RESPIRATION<sup>1,2</sup>

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### REGULATION OF RESPIRATION

*Respiratory centers.*—It has long been known, but never satisfactorily explained, that anesthetics depress the response of the medullary respiratory center to the direct effect of CO<sub>2</sub> without suppressing respiratory reflexes. Von Euler & Soderberg (1, 2) believe that CO<sub>2</sub>-sensitive receptors are located in the posterior medulla and are outside the pathways for respiratory reflexes. In support of this concept, they were able to detect slow potentials initiated only by CO<sub>2</sub> inhalation and depressed by chloralose. The origin of the potentials is not clear; they may be related to slow changes in pH, blood flow, blood volume, or cerebrospinal fluid pressure; further, there was not always good correlation between these potentials and respiratory minute volume so far as time, intensity, and direction were concerned. However, the evidence is convincing that they could be obtained only from that part of the medulla previously shown by others to be sensitive to electrical stimulation and to CO<sub>2</sub>-rich solutions injected locally.

The same investigators have detected rhythmic spikes in response to CO<sub>2</sub> inhalation from electrodes placed in the medullary center, isolated from all cranial nerves and the spinal cord. They conclude that medullary rhythmicity is dependent on CO<sub>2</sub> tension and that CO<sub>2</sub> can generate impulses in the complete absence of afferent impulses. Chatfield & Purpura (3) also noted that CO<sub>2</sub> inhalation increased the rhythmicity of the deafferented respiratory center. Histologic identification of medullary chemoreceptors has not yet been achieved; it is unlikely that they will be found to be attached to large blood vessels as are the carotid and aortic bodies. Tang (4), in support of Breckenridge & Hoff (5), has observed rhythmic, though distorted, breathing patterns, sufficient to sustain life for hours, after vagotomy and low brain stem section. However, he has also found a pneumotaxic center in the cat and

<sup>1</sup> The period covered by this review (approximately June 1952 to July 1953) has been marked by a considerable increase in interest in respiratory and pulmonary physiology. Merely to list the investigations published during the past year would require more space than is allotted for both comment and references in this review; on this account, the reviewer begs forgiveness for the omission of many important papers.

<sup>2</sup> The following abbreviations are used in this chapter: FRC (functional residual capacity); MBC (maximal breathing capacity); TV (tidal volume); WBC (white blood cells); DS (dead space). In order to conform with recommendations for standardization of symbols in respiratory physiology (*Federation Proc.*, 9, 602-5, 1950) P<sub>O<sub>2</sub></sub> and P<sub>CO<sub>2</sub></sub> are used throughout this paper to signify partial pressure or tension of O<sub>2</sub> or CO<sub>2</sub>; these symbols replace pO<sub>2</sub> and pCO<sub>2</sub> respectively.

localized it to the extreme dorsolateral portion of the anterior pontine tegmentum. Tang and others (3, 6) believe that medullary rhythmicity does not exclude more effective determinants of rhythmicity in the intact animals.

Hall (7), using 14 subjects, has confirmed the earlier work of Nielsen indicating that a threshold concentration of  $\text{CO}_2$  is necessary for respiratory stimulation under certain conditions. Hall's subjects were in a low pressure chamber at 22,000 ft. simulated altitude (321 mm. Hg); when they inhaled  $\text{CO}_2$ , their ventilation did not increase until alveolar  $\text{PCO}_2$  had increased from 26 (control) to 34 mm. Hg. Above the latter value, there was a linear relation between the increase in alveolar  $\text{PCO}_2$  and in ventilation. Winterstein & Gökhan (8) present further evidence for the "reaction theory" of respiratory regulation. They showed that the stimulant effect of  $\text{NH}_4\text{Cl}$  acidosis is produced by carotid body reflexes and that the central effect is a depressant one; although it decreased blood pH,  $\text{NH}_4\text{Cl}$  increased cerebrospinal fluid pH because of the ready diffusibility of  $\text{NH}_3$ . Presumably  $\text{NH}_3$  also diffuses rapidly into the cells of the medullary respiratory center, making it more alkaline, despite increased blood acidity.

Kaada & Jasper (9) found that respiratory inhibition followed electrical stimulation of certain areas in the temporal lobe, insula, and hippocampal and limbic gyri in man, and was often associated with impaired consciousness and sleepiness. The importance of conditioned reflexes in respiratory control has been emphasized by Freedman (10); a conditioned reflex may explain the increased breathing often noted immediately before the onset of muscular exercise.

*Carotid and aortic reflexes.*—There has been a revival of interest in the anatomy and physiology of the structures in the region of the carotid bifurcation. Chungcharoen *et al.* (11, 12, 13) have made a detailed study in dogs, cats, and rabbits of the blood supply of the carotid body and of the anatomy and hemodynamics of the anastomoses between the branches of the common carotid and those of the vertebral arteries and the circle of Willis. Although Wang *et al.* (14) disagree in certain respects, the differences may be resolved on the basis of the wide variations that are known to occur even among animals of the same species. Of considerable importance is the observation that branches of arteries supplying the carotid body also supply the superior cervical sympathetic and nodose ganglia in these three species. Drugs or perfusion fluids thought to be directed to the arterial supply of one of these three structures probably reach all three; this point must be considered in specific localization of chemical actions in this complex region.

Landgren & Neil (15) have made a major contribution in their observation that hemorrhage can cause a marked increase in chemoreceptor activity. It was originally thought that the metabolic rate of the chemoreceptors was so low that their activity would be uninfluenced except by extreme reduction in their blood flow. However, hemorrhage appears to lead to increased sympathetic vasoconstrictor activity which reduces blood flow through the carotid bodies so effectively that ischemic excitation develops. There is a bundle of

fibers which passes from the superior cervical sympathetic ganglion to the carotid bifurcation. Floyd & Neil (16) investigated the possibility that it might carry these vasoconstrictor impulses; it does, but apparently does not account entirely for the increased chemoreceptor activity during hemorrhage. Duke *et al.* (17) demonstrated that the chemoreceptors must have a low  $O_2$  requirement because no chemoreceptor discharge occurred during inhalation of CO until the HbCO concentration reached 75 to 80 per cent, at which time hypotension had developed.

Douglas (18) has shown that hexamethonium blocks carotid chemoreceptor response to nicotine, lobeline, and acetylcholine, but not to anoxia, cyanide, or KCl. He raises the possibility that some chemosensitive receptors may be intracellular and unaffected by hexamethonium although still responsive to anoxia, cyanide, and KCl. Any of the proposed mechanisms of chemoreceptor excitation still requires more precise histological justification.

Witzleb (19) has shown that chemoreceptor action potentials vary directly with temperature. Jarisch and co-workers (20) have used the technic of recording "impulse traffic" in the chemoreceptor fibers to demonstrate that KCl, veratrine, sodium citrate, adenosinetriphosphate, dinitrophenol, and embolization by lycopodium spores stimulate chemoreceptors. Although some believe that "conclusive information about the behaviour of the chemoreceptors can only be obtained" by this method (17), the electrical technics should not be used to the exclusion of determining the effects of these impulses upon body functions.

Heymans *et al.* (21, 22) have concluded that 5-OH-tryptamine and phenyldiguanide do not cause hyperpnea in the dog through chemoreceptor mechanisms, but Douglas & Toh (23) and Dawes *et al.* (24) have demonstrated that they do; it is difficult to reconcile these opposite results unless these drugs stimulate respiration through several mechanisms. Landgren *et al.* (25), found that papaverine and 2-benzyl-2-imidazoline (Priscoline) abolished all activity from both the carotid sinus and body by producing local anesthesia.

*Thoracic reflexes aroused by chemical agents.*—Some of the most fascinating of the respiratory reflexes are those initiated by a variety of chemical agents acting upon sensory receptors somewhere in the thorax (26). In general, the response consists of apnea, bradycardia or cardiac arrest, and hypotension. The list of chemicals which produce this effect is lengthened by the addition of cinchoninic acid derivatives [active in the cat and dog, but not in the rabbit (27)], antihistaminics [in cat, dog, and rabbit (28)], and 5-OH-tryptamine or serotonin [in the cat, but not in the dog (29, 30)]. The latter compound is of interest because it is the "vasoconstrictor principle" derived from platelets. It is reported that the effects of veratrine and aconitine can be prevented completely in the rabbit by prior intravenous administration of procaine (31), and the thoracic sensations produced in man by lobeline can be abolished by hexamethonium (32). The sensory receptors involved have not yet been identified; however, additional receptors have been demon-

strated in the pleura of man and in the tunic of the pulmonary artery (33).

*Other respiratory reflexes.*—Chatfield & Purpura noted that permanent respiratory failure followed section of the dorsal roots of  $T_1$  and  $C_4$  in four of 6 vagotomized cats and suggest that impulses excitatory to the respiratory center pass through the stellate ganglia (3). Calma has demonstrated that the diaphragm, unlike other skeletal muscles, can be influenced reflexly only through the integrating mechanism of the respiratory center and not by afferent impulses impinging on the cervical cord in the region of the phrenic motoneurons (34). Culver & Rahn (35) state that the excito-inspiratory reflex induced by negative pressure applied to the trachea is abolished completely by right vagotomy; however, although minute ventilation did not change when negative pressure was applied after vagotomy, the frequency did increase from 3.9 to 4.8 and the tidal volume decreased from 232 to 193 ml. Consequently these experiments do not exclude excito-inspiratory afferents originating in the chest wall.

Zissman found that simultaneous stimulation of several muscular branches of the sciatic nerve led to hyperpnea in the rabbit; this provides a new clue to the origin of the hyperpnea of muscular exercise (36). Others have studied the effects upon respiration and circulation of alterations in strength, duration, and frequency of currents applied to the central end of somatic nerves (37), the effect of ischemia and chemical stimulation of the intestine upon respiration (38), the characteristics of pulmonary stretch receptors (39), and the effect of unilateral phrenic block (40).

Peltier (41) believes that reflex closure of the upper airway can occur when hyperventilation is induced during sleep; this mechanism may act to prevent acapnia. Widdicombe has studied the properties of rapidly adapting mechanoreceptors in the trachea of the cat (42).

#### EVALUATION OF PULMONARY FUNCTION

The tremendous literature in this field illustrates well the impact of physiology upon clinical medicine. Recent reviews will serve to orient the reader in this field (43, 44, 45). Gilson & Oldham have emphasized the need for multiple tests of pulmonary function and suggest the use of Fisher's discriminant analysis, which provides a single index maximizing the difference between any two groups of results in relation to the scatter within them (46). Galdston *et al.* (47) have studied 19 individuals in the third to eighth decades who had no clinical evidence of cardiopulmonary disease and found a number of deviations from values obtained in healthy young men; this emphasizes both the sensitivity of some physiological tests and the need for normal values for all age groups. Anderson *et al.* (48) have studied normal individuals living at 5000 ft., and Cugell *et al.* (49) have established normal values for women during pregnancy.

*Lung volumes and ventilation.*—Normal subjects in the maximal inspiratory position can inhale 150 to 300 ml. more after blowing against 40 mm. Hg pressure (50); it might be of interest to use this test, which depends upon

exclusion or expression of blood from the lungs, in patients with pulmonary congestion. Campbell has studied the effect of pneumothorax on vital capacity (51). Lowell *et al.* (52) have described a modified Donald-Christie system to study continuously the changes in FRC<sup>2</sup> that occur during administration of aerosols of histamine or allergens. Bjorklund & Dahlstrom (53) have analyzed errors in the measurement of FRC by the helium closed-circuit method. Dejours & Rahn have described a method for measuring residual volume by gas expansion during decompression from 1.5 to 2.0 atmospheres (54). Lanphier has described a quick, approximate method for estimating the residual volume/total lung capacity ratio using the N<sub>2</sub> meter and requiring only a single breath of O<sub>2</sub> (55).

Pappenheimer *et al.* (56) approached the dead space problem by an ingenious technic in which alveolar gas tensions were maintained at a constant level during low O<sub>2</sub> breathing; this was achieved by varying rate and depth of breathing so as to keep ear oximeter readings at a constant value. Calculations from data obtained over a wide range of tidal volumes indicated a relatively constant DS.<sup>2</sup> Recalculations of Haldane's original data showed them to be consistent with constant DS values.

Wade & Gilson (57), by a mechanical device attached to the fluoroscope, have followed the movements of the dome of the diaphragm and recorded these simultaneously with the spiogram. They made the interesting observation that in 20 of 48 normal subjects, the diaphragm rose to a higher position on deep inspiration than on quiet inspiration, because of the lifting action of the thorax.

Proctor has reported further pneumotachographic studies in normals and patients with pulmonary disease (58). Morrow & Vosteen have devised a portable pneumotachograph and give normal values for air flow in dogs (59). Peltier & Visscher (60) emphasize the need for standard conditions and resistance in the upper respiratory tract in making measurements of tidal volume. Boothby *et al.* (61) have made a careful study of N<sub>2</sub> elimination from the body over long periods, using the N<sub>2</sub> meter. Boothby has again emphasized the changes that can occur in alveolar N<sub>2</sub> concentration during hyper- or irregular ventilation (62). Hall *et al.* (63) showed that loud speaking can produce hyperventilation and decreased arterial PCO<sub>2</sub>, a warning to orators!

Van Veen *et al.* (64) have used a closed circuit O<sub>2</sub>-N<sub>2</sub> system to measure FRC and distribution of inspired gas, determining the N<sub>2</sub>/O<sub>2</sub> ratio by measurement of specific heat conductivity. Becklake (65) found the "lung clearance index" (liters of ventilation needed to wash out each liter of FRC) to be a simple and satisfactory way of separating normals from patients with emphysema. Wade & Gilson (57) studied the diaphragm in the lateral recumbent positions. The "down" hemi-diaphragm was higher and moved more on inspiration than the "up" hemi-diaphragm; this provides a radiologic confirmation of Fowler's finding of increased turnover rate in the "down" lung.

*Diffusion.*—Campbell & Tomkeieff (66) indicate that internal lung surface can be calculated from scanning of Gough's whole lung sections (67) by



an electronic device. Low (68) has obtained electronmicrographs of the respiratory areas of the rat lung which show that endothelium forming the capillary wall is distinct from pulmonary epithelium lining the alveolar wall: each layer has an average thickness of about 0.1–0.2 $\mu$ .

Bates (69) has studied the amount and percentage of CO uptake during a two-minute, steady-state period in normal individuals during rest, hyperventilation, and exercise, and in patients with emphysema; this test may be useful in estimating the diffusing characteristics of the lung. Hatch (70) has discussed the theoretical considerations concerned in CO uptake at rest and exercise. Longmuir & Roughton have measured the rates of diffusion of CO and N<sub>2</sub> in a homogeneous solution of protein (30 to 40 per cent hemoglobin) and found these to be approximately 0.1 to 0.3 of the rate in water (71).

Williams (72) has measured A-a gradients in supine, lightly anesthetized dogs and in unanesthetized dogs in the lateral recumbent position. Riley *et al.* have extended their studies of D<sub>O<sub>2</sub></sub> to patients with sarcoidosis (73) and mitral stenosis (74). They believe that the calculation of D<sub>O<sub>2</sub></sub> may be erroneous unless the A-a gradient is at least 6 mm. Hg., and that the actual D<sub>O<sub>2</sub></sub> may be underestimated if there is variation in permeability of the pulmonary membrane for O<sub>2</sub> in different parts of the lung. Malmström & Michas (75) found that blood drawn from a catheter "wedged" in the pulmonary artery is considerably higher in P<sub>O<sub>2</sub></sub> and lower in P<sub>CO<sub>2</sub></sub> than systemic arterial blood indicating that the former had come from a region with high ventilation/perfusion ratio such as would exist if the blood were drawn through a second set of capillaries.

Dale & Rahn (76), in a series of ingenious experiments, have determined the rate of absorption of various gases from a blocked area of the lung in normal or denitrogenated animals, while air or O<sub>2</sub> was supplied to the non-blocked lung.

*MBC, spiograms, and bronchspirometry.*—The errors in spiographic recording at high respiratory rates have been analyzed and a new spirometer devised to eliminate the inertia of the moving parts and the tendency of the water column to resonate (77, 78). Using the new instrument, maximal values for volume of ventilation were recorded in normal men at about 70 respirations/min.; the MBC in patients with emphysema was not dependent upon rate, above rates of 30/min.

The MBC test is an arduous one for a sick patient, and many investigators are experimenting with a single, forced, timed inspiration or expiration or both with or without recording on fast moving kymographic paper (79 to 83). To date, there is no agreement on technic or on measurement of the spiograms.

With the advent of the new Carlens catheter, which has minimal and equal resistance to air flow through the two channels (84), has come a renewed interest in the measurement of individual lung function. Several groups report extensively their technical and clinical experiences. Residual volumes have now been measured separately (85), and studies have been made during both air and O<sub>2</sub> breathing (86).

*Exercise tests and dyspnea.*—Welch *et al.* (87) have found that a simple step test can be substituted for treadmill exercise. Hugh-Jones (88) has devised a step test in which both height and rate of stepping are varied to compensate for differences in weight of patients. In order to arrive at the true ventilatory cost of the exercise, he has taken into account the resting ventilation, the ventilation in excess of resting ventilation in both the exercise and recovery periods, and the time of exercise; an index derived from these values correlated well with the dyspnea level in 228 patients. Miller (89) found that  $O_2$  inhalation before, during, or after severe muscular exercise did not change the cardiovascular response, or formation of lactic acid; experiments were not done with brief exercise periods, such as 100 yard dash. Exercise tests have been used by Larimi (90), Georg (91), and Erikson (92). Richards has contributed an excellent review of cardiac and pulmonary dyspnea (93).

*Mechanics of breathing.*—One of the most important recent developments in pulmonary physiology has been the better understanding of the mechanical factors in breathing. McIlroy & Christie (94) have studied the viscoelastic properties of normal and emphysematous lungs post mortem. The positive pressure generated in the occluded trachea on opening the thorax averaged 4.3 cm.  $H_2O$  in 17 normal lungs and 1.75 cm. in the 10 emphysematous lungs. The "index of viscous resistance" (the ratio of TV at 3/min. to TV at 15/min., for the same pressure gradient across the lung) was 1.18 to 2.18 in normal lungs and 3.12 to 5.55 in emphysematous lungs.<sup>2</sup> Since these values were rarely reduced by inhalation of  $H_2$ , they probably represent an actual increase in viscous resistance in the parenchyma rather than in the airway. McIlroy & Christie conclude that emphysema is characterized not only by a decrease in elastance but also by an increase in the viscous resistance of the pulmonary tissue. Dornhorst & Leathart (95) and Fry, Stead *et al.* (96, 97) have applied Buytendyk's technic of estimating changes in intrathoracic pressure by measurements of esophageal pressure. The latter group found that the emphysematous lung retains some retractive force and that the relationship between this retractive force and change in volume of the lungs on inspiration is approximately linear over the range of the tidal volume.

Affeldt *et al.* (98) have measured pressure-volume relationship of the thorax and lungs in patients convalescing from poliomyelitis and found that compliance was reduced though the FRC was approximately normal. Day *et al.* (99), realizing that lung injury arises from overdistension and not merely from high pressure, have explored the possibility of inflating atelectatic lungs by bursts of high pressure acting for such short periods that overinflation will not occur. They showed that 40 cm.  $H_2O$  pressure applied simultaneously to an atelectatic and a normal lung for 0.15 sec. opened the former and produced less inflation of the latter than did 30 cm.  $H_2O$  acting for 1.5 sec.

Hardung (100) has developed apparatus for measurement of the dynamic elasticity and viscosity of rubber-like materials; the technic of employing forced vibrations of 1 to 15 c.p.s. is similar to that employed by DuBois for

measuring viscous resistance and inertia of lung tissue (101). Other papers discuss the thermodynamics of rubber-like elasticity, the elasticity of biological tissues (102), and the structure of elastic tissue (103).

Campbell has studied electromyographically the abdominal respiratory muscles and found that they contract during forced expiration and toward the end of a maximal voluntary inspiration; thus they appear to limit the depth of a maximal inspiration (104). The mechanics involved in esophageal speech are outlined in interesting fashion by Bateman *et al.* (105). Barach *et al.* (106, 107) have devised an exsufflator and a mechanical cough chamber to assist patients in clearing the tracheobronchial tree of secretions. The exsufflator inflates the lung by negative pressure of  $-40$  mm. Hg. around the thorax. This is followed by decompression in  $0.06$  sec. through a  $5$  in. valve so that a high expiratory velocity results. They state: "since very vigorous, natural cough results in intrapulmonary pressures greater than those employed in the exsufflator, the danger of rupture of the lung would not be present beyond that which might occur in a moderately vigorous cough." However, lungs rupture because of distention and not because of pressure; in emphysema, different parts of the lung may have different pressure-volume curves and one must be careful not to overdistend any portion.

*Pulmonary function studies in clinical conditions.*—Physiological studies have been used in diagnosis and management of poliomyelitis (108, 109), in clarifying the causes of respiratory acidosis during anesthesia and thoracic surgery (110, 111), in studying impairment of diffusion and distribution in mitral stenosis (74, 112), asthma and emphysema (113 to 116), the effects of surgical procedures on the lungs (117, 118, 119), the changes induced by pneumoperitoneum (120, 121, 122) and positive pressure breathing (123).

#### MISCELLANEOUS FUNCTIONS OF THE LUNG

The primary function of the lung is that of gas exchange. Another function may be related to storage, sequestration, or destruction of white blood cells. Weisberger *et al.* (124) have demonstrated that the lungs selectively remove lymphocytes, tagged with  $P^{32}$ , from the circulation whether injected intravenously or into a systemic artery. Possibly lymphocytes, separated *in vitro*, are no longer normal even though their staining characteristics are preserved; if so, this is important to remember in determining the life span of lymphocytes by injection of radioactive cells. Bierman *et al.* (125) believe that the human pulmonary circulation contains large numbers of WBC and platelets<sup>2</sup> which may be discharged into the systemic circulation by the proper stimuli, one of which is epinephrine. The Valsalva maneuver produced a decrease in WBC count in left ventricular blood of man compared with simultaneously drawn right ventricular blood; the Müller maneuver produced a prompt increase in systemic arterial WBC count (126).

The origin of lung histamine has not been satisfactorily explained, but Mongar & Schild (127) have developed a method for total and quantitative release of histamine from minced lung; monoamines, especially decylamine, are powerful histamine-releasing agents. Clark *et al.* (128), studying tissue

adenosine deaminase levels have noted that cat lung has unusually high activity; they suggest that this enzyme may constitute a biological defense mechanism in association with receptors sensitive to adenosine. Other lung enzymes are discussed by Astrup (129) and Anfinson *et al.* (130). The significance of lung enzymes is not yet clear.

#### PULMONARY CIRCULATION

Gordon *et al.* (131), using an air bubble perfusion technic, conclude that A-V anastomoses in the pulmonary circulation of the rat and rabbit are only about 15 to 19  $\mu$  in diameter; no explanation is afforded for the passage of glass beads of much larger diameter. Rahn *et al.* (132, 133) have described the fluoroscopic anatomy of the heart and pulmonary vessels in the dog and have visualized A-V shunts following jamming of a catheter far into pulmonary artery. Tobin & Zariquiey (134) have obtained beautiful color photographs of the human pulmonary and bronchial vessels. Ardran *et al.* (135) have made a fine contribution toward clarification of the changes that occur in the pulmonary and systemic circulation during and after the first inflation of the lungs of fetal lambs. Ventilation with positive pressure produced an immediate fall in pulmonary arterial pressure, presumably by causing a lower resistance in that circuit. It will be interesting to learn whether initial ventilation with N<sub>2</sub> will produce the same effect.

The effect of changes in gaseous composition of alveolar gas and pulmonary blood upon pulmonary vascular pressures and resistance continues to attract considerable attention. Ventilation with CO decreases pulmonary artery pressure in the cat (136). Anoxia produces pure dilatation in the perfused, ventilated dog lung according to Aviado *et al.* (137) but, according to Stroud & Rahn (138) and Lewis & Gorlin (139), causes increased resistance to flow, probably mediated through sympathetic pathways when arterial O<sub>2</sub> saturation is greater than 55 per cent. Daly *et al.* (140, 141) have studied further the vasomotor fibers to the lungs. It seems important to establish that nervous pathways have not been damaged in perfusion experiments and to record precisely the degree of anoxia by measurements of arterial O<sub>2</sub> saturation. Several groups have found that different vascular responses may be expected at different levels of oxygenation in the dog (138, 139, 142). Peters & Roos (143, 144) found that resistance to blood flow through one lung breathing N<sub>2</sub> increased 1.3 to 4.5 times in the dog.

The effect of inhalation of low and high concentrations of O<sub>2</sub> (145, 146, 147), the effect of ergot derivatives (148) and khellin (149) have been studied in patients. Madoff *et al.* (150) reported studies on a girl who was well despite congenital absence of the right pulmonary artery. Carlens *et al.* (151) have found that the right or left pulmonary artery could be occluded by a catheter-balloon in unanesthetized man with no symptoms; this seems to eliminate stretch of a large pulmonary artery as the source of chest pain in pulmonary hypertension (152). Several papers deal with the pulmonary circulation in emphysema (153) and with permanent or temporary occlusion of the pulmonary or bronchial arteries (154 to 157).

## PULMONARY EDEMA

Courtice (158) has written an excellent review of pulmonary edema and pulmonary lymph flow. Courtice & Korner (159) found that anoxia per se (11 per cent  $O_2$  for 5 hr.) did not increase lung weight/body weight ratio in the rabbit but did predispose to pulmonary edema when large amounts of intravenous fluid were infused. Presumably anoxia contributes by producing systemic vasoconstriction and increasing pulmonary blood volume. Drinker's finding that anoxia causes increased pulmonary lymph flow with decreased protein content could be the result of hemodynamic changes (increased capillary pressure and transudation of fluid) rather than a change in pulmonary capillary permeability. Experimental pulmonary edema has been produced by rapid intracarotid infusions (160), by discrete, bilateral lesions in the preoptic region of the rat (161), by increased intracranial pressure (162), and by intracisternal injection of thrombin and fibrinogen according to the method of Cameron and De (see 163). In the latter two instances, hemodynamic studies indicate that it is not necessary to postulate that an increase occurred in pulmonary capillary permeability, because the pulmonary edema was associated with a marked rise of pulmonary capillary pressure. Sarnoff's work (164), (165) indicates that cerebral irritation can produce intense systemic vasoconstriction which shifts blood to the pulmonary circulation (which is not constricted by the sympathetic overactivity) and also forces the left ventricle to exceed its work capacity. Ganglionic blocking agents prevent systematic vasoconstriction and so prevent this and other types of pulmonary edema associated with systemic vasoconstriction. Aviado & Schmidt (166) studied pulmonary congestion and edema following steam injury to the lower respiratory tract. Araujo & Lukas (167) found that pulmonary "capillary pressure" in patients with mitral stenosis averaged 27 mm. Hg at rest and 42 mm. Hg during a 5 min. period of exercise. Since acute pulmonary edema occurred in only one instance (pulmonary "capillary pressure" of 57 mm. Hg), they believe that edema is prevented, not by protective pulmonary arteriolar constriction, but by thickening of the capillary basement membrane and pericapillary fibrous tissue.

Luisada (168) has studied further the use of alcohol vapor as an antifoaming agent, and Rosenbluth *et al.* (169) have tested a variety of antifoam agents, some of which reduced significantly the incidence of pulmonary edema following injection of large amounts of epinephrine in rabbits. The rate of uptake of fluid from the lung has been studied by Qualls *et al.* (170).

ARTERIAL  $O_2$  SATURATION AND TENSION

Lambertsen *et al.* (171) measured  $P_{O_2}$  (improved bubble equilibrium technic) and  $O_2$  saturation (gasometric and spectrophotometric methods) of arterial blood drawn from 15 healthy males breathing 4 to 20.9 percent  $O_2$ . An "*in vivo*"  $O_2$  dissociation curve was constructed, making corrections for  $P_{CO_2}$  and pH. Values for arterial  $O_2$  saturation were consistently higher by the spectrophotometric than by the gasometric technic, but Roughton's cor-

rections were not made for the errors in the latter method. Studies made upon the arterial blood of smokers showed an expected decrease in  $O_2$  saturation (93.6 per cent versus 97.0 per cent in nonsmokers), but an unexpected decrease in arterial  $P_{O_2}$  to 87 mm. Hg (nonsmokers 94.2). Cassels & Morse (172) found no alteration in the  $O_2$  dissociation curve of hemoglobin in 17 patients with polycythemia; the low arterial saturation that occurred in six of these patients bore no consistent relationship to hemoglobin concentration or blood viscosity.

Nahas *et al.* (173) using oximeter and oxygen electrode technics, found that a blood  $P_{O_2}$  of at least 400 mm. Hg was required to effect practically complete saturation of hemoglobin at  $37^\circ$  C. with a  $P_{CO_2}$  of 40 mm. Hg. Hickam & Frayser (174), using a spectrophotometric method upon blood equilibrated at  $25^\circ$  C. with gas having a  $P_{O_2}$  of 97, 146, 316, or 632 mm. Hg, found  $O_2$  saturations of 94.6, 97.4, 98.7, and 100 per cent respectively; these values are low even for blood equilibrated at  $37^\circ$  C. These data challenge the belief that blood equilibrated with 146 mm. Hg  $P_{O_2}$  at room temperature is virtually completely saturated. Before abandoning this belief, a careful analysis of errors in the spectrophotometric method for measuring  $O_2$  saturation in whole blood seems desirable; this should include consideration of plasma effects, nonspecific absorption due to scatter, and specific search for the presence of pigments other than Hb and  $HbO_2$ .

Roos & Rich have reported a spectrophotometric method for  $O_2$  saturation and content using the Beckman instrument (175). Of particular value are the specific instructions by Perkins *et al.* (176) for the conversion of oximeters into direct-writing recording instruments at minimal cost. Markus & Baumberger have made a detailed study of the factors which determine plasma  $P_{O_2}$  in the neighborhood of the  $O_2$  electrode when red blood corpuscles are present (177).

#### CARBON DIOXIDE AND pH

DuBois *et al.* (178, 179) have made important observations upon the alveolar  $CO_2$  and  $O_2$  during breathholding, expiration, and inspiration which have enabled them to show clearly the cyclic variation in alveolar gas composition during each breath; expiration is equivalent to breathholding and inspiration to alveolar gas dilution. They have also estimated the  $CO_2$  dissociation curve of dog lung; this tissue serves to minimize variations in alveolar  $P_{CO_2}$  during breathing and breathholding.

The effects of  $CO_2$  on ventilation (180) and on the electrocardiogram (181) in normal men have been restudied.  $CO_2$  tolerance and toxicity continues to be of interest (182). Busse *et al.* (183) achieved high concentrations of  $CO_2$  by stopping respiration (except for "diffusion respiration") in three anesthetized, denitrogenated, schizophrenic patients; one very serious reaction implicated the high  $CO_2$  tension, at least in part. However, Brown & Miller (184) found that respiratory arrest did not occur in dogs until the inspired  $CO_2$  was 60 to 65 per cent; blood pressure began to fall at 50 to 75 per cent but did not fall to zero until inspired  $CO_2$  was 90 per cent or more (which of



course necessitates anoxia). However, after inhalation of 30 to 40 per cent  $\text{CO}_2$  for 4 hr., sudden reduction in  $\text{CO}_2$  tensions in inspired air and arterial blood was accompanied by cardiac arrhythmias in all and by fatal ventricular fibrillation in 11 of the 15 dogs used (185). Boniface & Brown (186) found that even 5 to 10 per cent  $\text{CO}_2$  in  $\text{O}_2$  decreased the cardiac contractile force and systolic amplitude (myocardiograph) but report no control experiments using  $\text{O}_2$  alone. Platts, from a study of patients with pulmonary heart failure, believes that there may be a critical level of  $\text{Po}_2$  or  $\text{PCO}_2$  associated with fluid retention (187). Arends *et al.* investigated the effect of high concentrations of  $\text{CO}_2$  upon RBC and extracellular volumes (188).

Rosenthal's pH temperature correction factor has been confirmed by Graig *et al.* (189) but they have found that the factor for an individual may differ from the mean sufficiently to produce an error of 0.06 pH units.

#### EFFECTS OF HIGH AND LOW $\text{O}_2$ TENSIONS

Lambertsen *et al.* (190) have achieved the very difficult task of measuring arterial  $\text{O}_2$ ,  $\text{CO}_2$ , and pH, as well as cerebral blood flow and metabolic rate for  $\text{O}_2$  in normal men breathing  $\text{O}_2$  at 1 and at 3.5 atmospheres; their data clarify many previously controversial points. Arterial and internal jugular venous  $\text{PCO}_2$  were 39 and 50 at 1 atmosphere and 34 (because of moderate hyperventilation) and 53 mm. Hg at 3.5 atmospheres. Thus there is little reason to attribute  $\text{O}_2$  toxicity at this latter pressure to a high  $\text{PCO}_2$  in the brain, since the A-V  $\text{PCO}_2$  difference across the brain rose only 8 mm. Hg and the absolute level of cerebral venous  $\text{PCO}_2$  rose only 3 mm. At 3.5 atmospheres, the arterial  $\text{Po}_2$  was 2100, but the internal jugular venous  $\text{Po}_2$  was only 75 mm. Hg; the 6.5 ml. of dissolved  $\text{O}_2$  per 100 ml. blood was not enough to meet the metabolic needs of the brain because cerebral vascular resistance increased 55 per cent and cerebral blood flow decreased 25 per cent. Lambertsen believes that  $\text{O}_2$  toxicity is accentuated by  $\text{CO}_2$  inhalation largely because the latter produces an increase in cerebral blood flow so that less  $\text{O}_2$  is extracted from each unit of blood and consequently jugular venous  $\text{Po}_2$  and, presumably, cerebral  $\text{Po}_2$  rise considerably. Sonnenschein *et al.* (191) placed an  $\text{O}_2$  electrode in the cortex of cats exposed to  $\text{O}_2$  at 40 to 75 psi and found that seizures occurred only when there was a rapid and marked (ten- to fiftyfold) rise in brain  $\text{Po}_2$ . The tissue  $\text{Po}_2$  decreased with time, probably because of cerebral vasoconstriction.

Bean & Johnson (192, 193) found that hypophysectomy gave some protection against pulmonary damage produced by exposure of rats to high pressures of  $\text{O}_2$ ; they attribute this to a decreased production of adrenal cortical factors. Lambertsen *et al.* (194) believe that the hyperpnea caused by exposure to high pressures of  $\text{O}_2$  is most likely due to central accumulation of  $\text{CO}_2$ , owing to insufficient reduction of  $\text{HbO}_2$ . This hyperventilation lowers the alveolar and arterial  $\text{PCO}_2$ . That cerebral vasoconstriction occurs when arterial  $\text{PCO}_2$  is decreased and cerebral  $\text{PCO}_2$  is increased suggests that the  $\text{CO}_2$  effect on cerebral vessels is a precapillary one. Whitehorn & Bean (181) have compared the electrocardiographic changes produced in dogs by ex-



posure to  $O_2$  at 60 psi with those produced by exposure to 11.5 per cent  $CO_2$  and to 8 per cent  $O_2$ . Storstein has conducted a careful investigation of the effects of  $O_2$  inhalation upon the circulation in normal subjects and upon 49 patients with cardiopulmonary disease (145).

Stickney & Van Liere have reviewed the subject of acclimatization to low  $O_2$  tensions (195). Studies at high altitudes have been conducted by Tenney *et al.* (196) and Terzioglu *et al.* (197). The polycythemic response produced by discontinuous anoxia for 27 to 73 days was the same in sympathectomized and in normal dogs (198). Rats born at 3990 m. developed fatty degeneration of the liver which delayed growth and development or prevented survival; prevention of anoxia until after the first month of life prevented the hepatic lesion (199). Stacy & Hitchcock studied the effect of low  $P_{O_2}$  in the inspired gas on alveolar  $P_{CO_2}$  (200). Intrapulmonary pressures of 80 to 120 mm. Hg of  $O_2$  (maximum 250) could be tolerated by dogs decompressed to 72,000 ft. simulated altitude; these increased survival time (201).

#### ARTIFICIAL RESPIRATION

Swann *et al.* (202) have evaluated resuscitation procedures and the general principles of resuscitation. The ineffectiveness of artificial respiration in rats after drowning results neither from ventricular fibrillation nor from hemolysis, but from tracheobronchial block with water and foam (203). Methods have been devised for giving effective manual artificial respiration under circumstances which do not permit use of standard procedures (204).

Maloney *et al.* (205) have emphasized the importance of the negative pressure phase in mechanical respirators to improve the circulation of apneic patients in shock. In general, however, no hypotension results from the use of positive pressure resuscitators with a low mean mask pressure and proper pattern. Smith (206) has reported upon a patient who died after 18 years of partial or complete dependence on a body respirator. The diaphragm, chest, and abdominal muscles were completely replaced by fat or fibrous tissue. Death occurred from renal failure, caused by renal calculi, a complication of immobilization. Fischer *et al.* (207) have been successful in maintaining the life of dogs by the use of homologous lungs and a mechanical heart; heterologous lungs have not yet been employed.

#### DRUGS AFFECTING RESPIRATION

Whelan & Young found that both epinephrine and norepinephrine, given intravenously, produced an abrupt increase in depth and a slight increase in rate of respiration (208);  $O_2$  consumption was increased consistently by epinephrine and inconsistently by norepinephrine. The effects upon respiration of 3-hydroxy-*N*-methylnorphinan (Dromoran) (5), papaverine (209), salicylates (210), and nicotine and aminocordin (211) have been studied.

#### TRACHEO-BRONCHIAL TREE AND AEROSOLS

Lucas has reviewed bronchial dynamics and added thought-provoking comments on cough, hiccup, bronchiolar- and laryngospasm (212). A large

number of papers deals with bronchial obstruction or bronchial constriction. Actually none of the methods used in intact animals or man measures constriction of the smooth muscle or even bronchial obstruction; for the most part they measure distensibility of a system whose pressure volume characteristics are unknown initially and may change quickly for reasons other than bronchial constriction. Daly *et al.* (213) report that perfusion of anoxic or hypercapnic blood through the brain produces constriction of the bronchial musculature; this effect is opposite to that originating in the carotid and aortic bodies or in the bronchioles themselves. Hawkins & Schild (214) rated the effectiveness of isopropyl noradrenaline, epinephrine, norepinephrine, ephedrine, and aminophylline, in that order, as smooth muscle relaxants on human bronchial chains. Cordier (215) discussed the effects of mustard gas and Rakietyen *et al.* (216), the action of menthol and nicotine on ciliated epithelium. The physiological and pharmacological characteristics of liquid aerosols have been reviewed by Dautrebande (217).

#### METHODS AND APPARATUS

Methods have been reported for micro gas analyses (218), rapid measurement of plasma  $\text{CO}_2$  on 0.1 ml. samples (219) and of  $\text{O}_2$  in 2.0 ml. syringes (220), analysis in an infrared gas analyzer of  $\text{N}_2\text{O}$  extracted from blood (221), measurement of expired  $\text{CO}_2$  (222) by the mass spectrometer, quantitative determination of radioactive  $\text{CO}_2$  in alveolar gas or arterial blood (223), the spectrophotometric determination of blood CO, using the Evelyn colorimeter (224), and for the use of the oximeter to evaluate pulmonary function (225). Hausler & Lex (226) and Hensel (227) have devised new gas valves. Balchum *et al.* have measured the permeability of the Douglas type bag to respiratory gases (228).

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# THE DIGESTIVE SYSTEM<sup>1</sup>

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## FOOD INTAKE: SALIVARY SECRETION

A valuable contribution to the subject of salivary secretion has come from Emmelin & Muren (1), who have devised an ingenious technique for studying in cats the sensitivity of the submaxillary glands to various drugs over long periods of time. The oral papilla of the duct was cannulated in the anaesthetised animal, anaesthetics and drugs being administered intracardially. No other operative procedures being required, the animals were allowed to recover at the end of the experiment and could be studied in this way daily over long periods of time. It was shown that ether and morphine increased the sensitivity of the salivary glands to sialagogue drugs, because of the release of epinephrine (adrenaline) and norepinephrine (noradrenaline) which they cause from the adrenal medulla. Chloralose or the barbiturates had no such effect. When the sensitivity of the submaxillary gland to epinephrine was studied daily after section of the chorda tympani, the response was found to increase to a maximum in about two weeks. The daily administration of atropine to the animal sensitised the normal gland of the opposite side until it eventually equalled the denervated gland in its response to epinephrine. When the daily doses of atropine were discontinued the sensitivity of the intact gland gradually declined to its original level. When daily doses of pilocarpine were given, the sensitivity to epinephrine of the denervated gland rapidly declined to the low level of the intact gland, the sensitivity of which to epinephrine was hardly affected by the pilocarpine. When pilocarpine was discontinued the sensitivity of the denervated gland to epinephrine rose to the pre-pilocarpine level in about two weeks. The epinephrine-sensitivity of the denervated gland was similarly reduced to that of the intact gland by daily doses of carbachol (choline chloride carbamate), and recovery followed when the drug was discontinued. Daily doses of epinephrine reduced the sensitivity to this drug of both the denervated and normal glands. It seems clear from this work that a submaxillary gland deprived by section of the chorda tympani of its normal stimuli undergoes some slow change which leads to a supersensitivity to sialagogue drugs (in this case adrenaline). The process is reversible by daily application of a parasympatheticomimetic stimulus (pilocarpine, carbachol). The same technique was subsequently used by Emmelin (2) to investigate the nature of the well-known phenomenon of "paralytic secretion" in the salivary glands. There are two prerequisites for the appearance of this secretion: (a) a supersensitivity of the gland cells to stimuli, and (b) the appearance in the blood of some sialagogue. The phenomenon is thus essentially similar to paradoxical

<sup>1</sup> The survey of literature pertaining to this review was completed June, 1953.

cal pupillary dilatation and "pseudomotor contracture." In the case of the salivary glands, the supersensitivity is classically produced by denervation, but it can also be produced in the intact gland by daily doses of atropine [Emmelin & Muren (1)]. The sialogogue which appears in the circulation in classical paralytic secretion is epinephrine or norepinephrine, released from the adrenals; a paralytic secretion in a denervated gland is only obtained under experimental conditions in which the output of these substances from the adrenals is high (e.g., morphine anaesthesia), and a paralytic secretion in these circumstances is brought to an end by exclusion of the adrenals. Emmelin's paper presents convincing evidence from cross-circulation and other experiments that this is the explanation of the phenomenon of paralytic secretion.

Squires (3) obtained evidence of an unusual character suggesting that salivary amylase activity in humans is influenced by the nature of the diet, from observations of four racially different groups living on different diets in Bechuanaland. One group was transferred for three months from a carnivorous to a carbohydrate diet, during which the amylase activity of the saliva showed a great increase.

Witt *et al.* (4) found that electrocoagulation of the anterior hypothalamic region in dogs led to a complete absence of thirst postoperatively, with rapid deterioration of the animals in the absence of therapy; while Hill and co-workers (5) showed in dogs that stimuli from the small intestine, excited by hypertonic solutions or distension, inhibit to some extent the desire to eat.

The mechanism of swallowing has excited comparatively little attention recently, so that the study of the pressure changes in the oesophagus during swallowing made by Butin and associates (6) is the more welcome for that. Using a miniature electrical transducer recorder in the oesophagus, they observed an initial negative wave, followed by three positive pressure waves, only the last of which was a true peristaltic wave passing the recorder. In patients with cardiospasm, it is interesting to note that considerable spontaneous motility was observed, as well as extremely variable responses in pressure after swallowing; a co-ordinated distally travelling wave of peristaltic type could not be identified.

#### GASTRIC SECRETION

As is to be expected, studies of the mechanisms of gastric secretion, and the possibility of its inhibition or modification in various ways has engaged the attention of a large number of workers. Doig, Wolf & Wolff (7) studied gastric function in a "decorticate" patient provided with a gastric fistula following extensive cerebral damage. Gastric movements were normal in general character although no inhibition of gastric motility was seen in nausea, but secretion was continuous and greater than normal and there was no response to insulin.

Macdonald & Spurrell (8) were enabled to prove directly that the pectin meal used in their Serial Test Meal method of studying human gastric func-

tion does not in fact stimulate the cephalic phase of secretion. They sham-fed the pectin meal to a patient with achalasia of the cardia and a gastrostomy and failed to obtain a secretory response, although a response was obtained to an ordinary meal. Hunt & Macdonald (9) showed that not only the extent but also the character of the secretory response to the pectin meal varied with its volume.

The nature of the humoral agent involved in the "intestinal phase" of the response of the stomach to a meal has hitherto received little attention. Sircus (10) shows that it is probably a hormone. The response of a Heidenhain or denervated pouch in the dog to irrigation of a Thiry-Vella loop with dilute acid or intestinal chyme was abolished by previous application of procaine to the mucosa, although this agent itself had no effect on the behaviour of the pouch. This study adds further evidence to the view that the release of hormones from the stomach and small intestine may be under the control of the intramural plexuses.

Flood *et al.* (11) report on their experience with an improved version of the tubeless method of gastric analysis, the patient being given a cation exchange resin containing quinine. In the presence of free HCl the resin liberates quinine-HCl which is absorbed and excreted in the urine, where it can be estimated. They conclude that the test is a reliable one for the detection of achlorhydria. Only one definite error was made in 100 cases.

Dragstedt and associates (12) continued their interesting studies on the mechanisms of gastric secretion in dogs using the method of continuous collection of gastric juice over long periods of time. When the denervated pyloric antrum was transplanted into the colon, secretion from a Heidenhain pouch in the same animal remained at a low level until the colon was obstructed, producing distension and increased motility of the antral pouch. Hypersecretion then followed, but disappeared when the obstruction was relieved. Dragstedt *et al.* (13) also showed that in dogs with innervated total gastric pouches and oesophageal-intestinal anastomosis removal of the antrum led to a 23 per cent reduction in the daily output of HCl; daily acid output was virtually abolished by crushing the vagus. The same authors further report that in patients with gastrojejunal ulcers following partial gastrectomy, the pyloric antrum having been left, hypersecretion persisted after the antrum was later removed. Woodward & Dragstedt (14) reported that in dogs from which the pyloric antrum had been removed and a Heidenhain pouch made as long as 5 yr. previously, depression of the gastric secretory response to a meal was still apparent, although the sensitivity of the pouches to a histamine test had not altered.

Continuous collection of gastric juice in dogs was also used by Schmitz *et al.* (15) to study the effect of gastro-jejunostomy on the response of the Heidenhain pouch. The daily volume of secretion markedly increased following the operation and declined again when the anastomosis was taken down. Storer and associates (16) found that the response of Heidenhain pouches in dogs to meals was increased by vagotomy, apparently because of the longer

time available for gastric digestion in the absence of normal gastric motility and emptying; but the explanation may not be as simple as this, for Code (17) observed that in pouch dogs responses of longer duration to parenteral stimuli such as alcohol and histamine were obtained after vagotomy.

The problem of the possible participation of the vagi in the release of the gastric hormone can be seen to underlie several of the investigations mentioned above; and it was a major consideration in the intensive study reported by Burstall & Schofield (18) who studied the secretory effect of psychic stimulation and insulin hypoglycaemia on Heidenhain gastric pouches in dogs, using a method of irrigation of the pouch which enabled them to measure very small responses of acid and pepsin. They found that both methods of stimulation caused a very small but quite definite secretory response from the pouches, a phase of depression being detected in the insulin test. This was observed also by Karvinen & Karvonen (19) and Olsen (20) and is due apparently to sympathetic excitation preceding the parasympathetic response. Burstall and Schofield interpreted their findings in favour of a release of gastric hormone from the main stomach rather than a vagal component in the sympathetic supply to the pouch. Burstall *et al.* (21) also report an unsuccessful attempt to produce long-term stimulation of gastric secretion in Pavlov pouch dogs by anastomosis of the proximal end of the phrenic nerve to the distal end of the vagus, as near to the stomach as possible. Although nerve impulses of phrenic type could be recorded in the vagus nerve some distance below the anastomosis, there was no evidence of continuous stimulation of the Pavlov pouch even after the lapse of many months.

How far we still are from a complete picture of the mechanisms involved in normal gastric secretory responses is evident not only from the foregoing discussion but also from the report by Porter, Longmire & French (22) of a neurohumoral mechanism of hypothalamic origin for stimulation of gastric secretion in monkeys. Electrical stimulation of the anterior hypothalamus caused gastric secretion of prompt onset and early decline, via the vagi; but stimulation of the posterior hypothalamus caused a stimulation of gastric secretion apparently due to the liberation of ACTH (adrenocorticotropin) and in turn cortisone. The response did not reach its peak for  $2\frac{1}{2}$  to 3 hr. and declined to normal in about 5 hr. A gastric secretory response could also be elicited by intravenous injection of ACTH, cortisone, or epinephrine, and the effect of electrical stimulation was prevented by adrenalectomy. Insulin injection gave a secretion in which the characteristics of both types of response could be detected. Insulin administered to vagotomised or adrenalectomised animals gave only one or the other of the two types of response.

The stimulant effect of cortisone and ACTH on gastric secretion has been noted by others. Zuriran, Kark & Dragstedt (23) found that a sustained rise in acid output by pouch dogs resulted from the daily administration of ACTH; however Welbourn & Code (24) observed a slight but significant decrease in gastric acidity of pylorus-ligated rats when cortisone was administered. The incidence of ulceration was unchanged. Adrenalectomy also de-

creased the secretion of acid. Eastcott *et al.* (25) contribute to the view that uropepsinogen excretion may reflect the level of ACTH-cortisone activity, by their observation that these substances increased uropepsinogen excretion in patients. Incidentally, they report that uropepsinogen excretion continued after complete gastrectomy in six of their subjects, and vagotomy did not influence uropepsinogen output. These findings are hardly in accord with the generally held view that uropepsinogen originates in the gastric gland cells.

Linde, Öbrink & Ulfendahl (26) showed that enterogastrone primarily inhibits gastric secretion by reducing the volume output of the juice; the acidity therefore declines, but not to a greater extent than would be expected by reason of this.

Hammar & Öbrink (27) report the interesting observation that in pouch dogs exercised on a treadmill, gastric secretion in response to histamine or food was inhibited. Rise in temperature was not the prime factor; inhibition could be transferred by blood transfusion from an exercised dog to a resting animal. The nature of the humoral agent was not elucidated; but these findings inevitably call to mind the work of Verney and his pupils on the release of antidiuretic hormone from the pituitary by exercise and other emotional stress.

The role of intracellular histamine in the response of the parietal cell is a problem which has stimulated several investigations during the past year. Sircus (28) showed that the antihistaminase drug B<sub>1</sub>-pyrimidine (2-methyl-5-amino-methyl-6-amino-pyrimidine) potentiated the gastric secretory response in dogs and cats to a variety of stimuli of nervous or chemical nature, without itself exciting gastric secretion, suggesting that the histamine in the parietal cell is concerned in its response, however excited. The distribution of histamine and histaminase in the gastrointestinal tract of animals has received fresh attention. Haeger & Kahlson (29) showed that histamine and histaminase are abundant throughout the gastrointestinal tract of the cat, except in the stomach, where histaminase is absent. This is a much-needed confirmation of an interesting and possibly significant fact, first pointed out by Best & McHenry in 1930. Haeger & Kahlson (29) found that there was no apparent relation between the histamine and histaminase activity in different regions, and seven days fasting did not alter the amount of the enzyme present in the mucosa. Later Haeger, Jacobsohn & Kahlson (30) observed that removal of the pituitary or adrenals in cats caused a profound reduction in the amount of histaminase in the gastrointestinal tract, without effect on the histamine content. Feldberg & Harris (31) applied the Linderstrøm-Lang procedure of making frozen serial sections in a horizontal plane through the gastric mucosa of the dog to work out the distribution of histamine in the various levels. In the body of the stomach, two regions of concentration of histamine were demonstrated, one in the parietal cells, the other in the muscularis mucosae. In the pyloric region only one "peak" was found, in the region of the glands. In the duodenum there

were two peaks, one for the villi, the other for the muscularis mucosae; jejunum was similar to duodenum. In the ileum there was one peak, corresponding to the glands. Smith (32) showed that "compound 48/80," a condensation product of *p*-methoxyphenylethylmethylamine and formaldehyde, which releases histamine and stimulates gastric secretion, liberates only a small fraction of the total gastric mucosa histamine; the rest is bound or otherwise resistant to the action of the drug.

Interest in the detailed mechanism of acid production in isolated mucosa preparations continues. Rehm (33) showed that the electrical resistance of the dog's gastric mucosa decreases when secretion is stimulated, and subsequently the same author (34) proposed a new hypothesis of gastric secretion, according to which the surface epithelial cells secrete the H ion of the gastric acid and the parietal cells the Cl ions. Davenport & Chavré (35) studied the rates of lactic acid production, acid secretion, and oxygen usage in frog gastric mucosa at various  $O_2$  tensions, with and without the addition of histamine and glucose. They conclude that at low  $pO_2$  glycolysis can contribute energy for acid secretion, and that the efficiency value  $Q_H/Q_{O_2}$  is 4 or less. The same is apparently true of the mouse stomach [Davenport (36)]. Hogben (37) showed that the rate of acid production by isolated frog gastric mucosa bathed in  $HCO_3$ -free fluid is doubled if either surface is exposed to 5 per cent  $CO_2$ . The powerful carbonic anhydrase inhibitor "6063" (see p. 162) in a concentration of 10mM failed to abolish spontaneous acid secretion and did not block the potentiation of secretion by  $CO_2$ .

Villarreal (38) reports the interesting fact that the production of pepsin and acid by isolated mouse stomachs is stimulated by distension and such stimulation is abolished by addition of 4 per cent procaine to the internal fluid, although the basal rate of secretion is not affected. Atropine and hexamethonium failed to prevent stimulation by distension.

The gastric mucosa would hardly seem a promising field for the application of physical techniques to cellular studies, but Engström & Malmstrom (39) were able by x-ray absorption analysis to compute the dry weights of single chief and parietal cells in the gastric mucosa. The chief cells have about 2.3 times the mass of the parietal cells, indicating a much higher water content of the latter (85 per cent).

#### PEPTIC ULCER: SECRETORY INHIBITORS

An intensive search continues for drugs which will effectively inhibit gastric secretion and may therefore be worthy of clinical trial in peptic ulcer patients. This arduous work seems to have been largely unrewarding. The conclusions of Kirsner & Palmer (40) from their trial of 16 such substances in human patients seems to sum up the position. The inhibitory action of antisecretory drugs on gastric secretion in man varies widely, especially after oral administration, both in different individuals and in the same individual on different occasions. There is a similar variation in the occurrence



and severity of side-effects, and the more effective antisecretory drugs have the more pronounced side-effects. None of the drugs available at present consistently produces anacidity without side-effects in man. Robertson & Grossman (41), using pouch dogs, screened 204 compounds over a period of 5 yr. These consisted of atropine derivatives, sympathomimetics, and antihistaminics. A few of the latter had definitely antisecretory properties. Of the total only 36 produced statistically significant inhibition, and in most cases the dose required made it unlikely that clinical trials would be worthwhile. Visscher, Vander Brook & Tazelaar (42) compared the gastric secretory properties of epoxytropine tropate methyl bromide (Pamine bromide), methantheline bromide (Banthine bromide), atropine sulphate, and scopolamine hydrobromide. The first of these was shown to have some antiulcer power in dogs and starved rats. Bayer, Plummer & Bradford (43) found that Prantal (N,N-dimethyl-4-piperidylidene-1,1-diphenylmethane methyl sulphate) was ineffective against symptoms in peptic ulcer patients on an ordinary diet unless given in high dosage (500 to 600 mg. every 6 hr.). Relief was attended by mild atropine-like side-effects. McCarthy *et al.* (44) report favourably on the properties of Darstine, a new quaternary ammonium compound (5-methyl-4-phenyl-1-(1-piperidyl)-3-hexanol methobromide). It apparently acts by a direct effect on the cells, and was effective against histamine secretion, and the basal secretion. Other studies on such compounds included those of Kirsner, Levin & Palmer (45) and McManus, Bochev & Beyer (46). Grover and co-workers (47) showed that the application to gastric pouch mucosa in dogs of 0.5 per cent sodium lauryl sulphate causes a striking inhibition of gastric secretion, lasting up to 3 hr. after administration. Mucoprotein secretion was unaffected; pepsin was inactivated by the sodium lauryl sulphate. Acid production by the parietal cells was apparently directly inhibited. Robertson & Grossman (48) produced inhibition of gastric secretion by irrigation of several antihistaminics into dog gastric pouches but attribute the effect of these to irritation of the mucosa since the secretion was mucoid and bloody after application of the drugs. Steinfield (49) completely suppressed gastric secretion in dogs for three months by four to seven exposures of the mucosa to the emanation from radio-krypton since it was first introduced by inflation of a balloon in the stomach with the gas for the duration of the half-life of the isotope (78 min.). The mucosa remained grossly normal in one of the two dogs so treated; the other showed pathological changes. The blood picture was unaffected.

The incidence of ulceration in pylorus-ligated (Shay) rats continues to be used in investigations on antiulcer substances, although the method has been criticised on various grounds since it was first introduced. The work of Segal, Haroutunian & Morton (50, 51) emphasises some of the pitfalls in its use by the indiscriminating. They showed that while large doses of a commercial enterogastrone extract completely protected rats against ulceration, this was associated with a toxic or shock-like reaction, which may well have been the case of the failure to obtain ulcers, because of the resultant depression of

gastric secretion. They also observed that urogastrone extracts made with water and not urine as the starting material gave significant protection against ulceration, possibly due to the presence of a contaminant derived from the initial precipitation in the method.

Sauvage and associates (52) presented a study of some factors influencing jejunal ulceration in a new type of surgical preparation. In dogs an innervated pouch of the entire acid-secreting region of the stomach was drained into the second part of the duodenum through a jejunal tube. Ulcers occurred in the latter in a few weeks. Vagotomy of the pouch did not decrease the incidence of ulceration, but antrumectomy did. A combination of the two procedures protected the dogs against jejunal ulceration.

Grover & Maaske (53) found the Shay rat suitable for tests of local anti-ulcer agents such as antacids, antipepsins and coating agents, e.g., gastric mucin. Sodium lauryl sulphate was demonstrated to be an effective antiulcer agent. Nickerson & Curry (54) also used the Shay rat for this purpose. They showed that oral administration of emulsified methylpolysiloxanes, which form tenacious hydrophobic surface films would protect the Shay rat, and guinea pigs given histamine-beeswax injections, from ulceration.

One of the most striking findings in the field of antisecretory drugs has been the demonstration by Janowitz, Colcher & Hollander (55) that the compound "6063" (2-acetylamino-1,3,4-thiadiazole-5-sulfonamide) an inhibitor of carbonic anhydrase 440 times more potent *in vitro* than sulphanilamide strongly depresses acid gastric secretion stimulated by histamine in dogs. The latent period was 20 to 80 min. and inhibition, though considerable, was never complete. The authors remark that this failure to inhibit acid secretion completely may be due to a failure to attain a sufficient concentration of inhibitor in the parietal cell or may indicate the extent to which the hydration of carbon dioxide can proceed in the virtual absence of carbonic anhydrase. Rehm *et al.* (56), however, claim that in anaesthetised dogs gastric secretion stimulated with histamine with or without methacholine can be completely inhibited with 6063, and find that concomitantly the expected fall in electrical potential difference across the mucosal surface occurs.

The relation of gastric acid to ulcer pain has been investigated by Ruffin and co-workers (57) who fed 0.1 N HCl, with or without barium, to ulcer patients and correlated the occurrence of pain with the radiological findings. They suggest that abnormal motility is a factor in the production of the pain as well as acid.

#### EMESIS: GASTRIC MOTILITY

Wang & Borison (58) reviewed their work on emesis, leading to the demonstration of the existence of a medullary chemoreceptor trigger zone for vomiting. Wang & Glaviano (59) utilized the procedure described in the review by Wang & Borison for determining the locus of action of any emetic

agent, to investigate morphine and Hydergine.<sup>2</sup> Eighty per cent of dogs vomited after 0.5 mg./kilo intravenously of morphine, but after successful ablation of the trigger zone none vomited after as much as 5 mg./kilo intravenously. Similar results were obtained with Hydergine. It was difficult to produce vomiting with either drug on oral administration in intact animals, and impossible after removal of the trigger zone. It is concluded that the emetic action of both drugs is purely central.

Walder (60) presented an interesting study of the reactions to drugs of freshly removed muscularis mucosae from human operation specimens. Evidence was obtained of regional differences in motility, sensitivity, and type of response, and indications were found that the submucous plexus may contain nerve cells, some of whose endings are cholinergic and others adrenergic. Another valuable study on the reactions of intestinal muscle to drugs is that of Evans & Schild (61) who determined the reactions to drugs of plexus-free cat jejunal muscle obtained by separating the muscle layers after Magnus' original method, the absence of ganglion cells from the preparations being checked by serial histological sections.

Rhythmical contractions of ganglion-free circular muscle were often recorded in the absence of drugs. Nicotine stimulated ganglion-free muscle and barium potentiated the effect of nicotine. In ganglion-free preparations which had been stimulated by eserine and acetylcholine, addition of nicotine produced a transient inhibition preceding stimulation. Low concentrations of eserine failed to stimulate ganglion-free preparations but regularly stimulated plexus-containing intestinal segments. Barium produced rhythmical contractions in ganglion-free preparations, but in intact preparations the contractions were more powerful and culminated in spasm; its action is therefore considered to be partly muscular and partly nervous. Acetylcholine stimulated both normal and ganglion-free preparations, but the threshold in the latter was generally higher; in the presence of eserine and barium the thresholds were about the same.

A number of miscellaneous studies have been made on gastric and intestinal motility in intact animals. Louckest, Quigley & Romans (62, 63) recorded the sounds produced by the passage of gastric contents through the pyloric sphincter in unanaesthetised dogs and related them to the emptying cycle. The duration of the sounds was shorter than the actual emptying time during the cycle but correlated well with other evidence of emptying; they are produced by vibration of mucosal folds, turbulence of the chyme, and in the fasting animal by the expulsion of gastric juice and air. In another study with similar techniques Quigley, Hudgins & Ellis (64) showed that the introduction of  $\text{NaHCO}_3$  into the duodenal bulb of dogs increased tone and motility there; introduction into the stomach similarly increased activity of the antrum, sphincter, and bulb; water had no such effect. Northup, Stickney &

<sup>2</sup> Hydergine is the trade name for a mixture of hydrogenated ergot alkaloids: dihydroergocornine methanesulfonate, dihydroergocristine methanesulfonate, and dihydroergocryptine methanesulfonate.

Van Liere (65) demonstrated the depression of gastrointestinal motility in dogs produced by administration of dicyclomine (Bentyl) and methantheline (Banthine), using the charcoal-acacia marker method; and in a similar study Fang, Northup & Van Liere (66) observed the combined effect of tetraethylammonium and anoxia on intestinal motility in rats. Van Aradel & David (67) used a similar method in rats, and a faecal-pellet-counting method in rabbits to demonstrate that  $\alpha$ -DL-acetylmethadol was six times as effective as morphine in suppressing propulsive motility. Chapman *et al.* (68) compared in humans the effects on gastrointestinal motility of methantheline (Banthine), tincture of belladonna, and placebos, using serial x-rays after a barium meal. Tincture of belladonna was little better than the placebo, but methantheline had a significant effect. The effect of methantheline on pain and antral motility in peptic ulcer patients was also studied by Hightower & Gambill (69). They obtained a significant positive correlation between antral contractions and the occurrence of pain. Methantheline relieved the pain and inhibited the contractions. In two patients however with continuous ulcer pain, the contractions were inhibited but the pain was not relieved. Those who like brown bread will rejoice in the observation of McCance, Prior & Widdowson (70) that brown bread stimulates more saliva and gastric juice in human subjects than does white bread, and is evacuated from the stomach and passed through the intestines more rapidly. The residues leave the colon more rapidly than do those of white bread.

#### INTESTINAL ABSORPTION

A revival of interest appears to be taking place in the mechanism of absorption of water-soluble substances from the small intestine, using isolated intestinal loops so that the substances accumulating in fluid surrounding the intestine can be compared with those inside. Wiseman (71) introduced an ingenious apparatus on these lines, showing with it that the L-isomers of alanine, phenylalanine, methionine, histidine, and isoleucine were transported across the wall of rat intestine against a concentration gradient. There was no such transport of the D-isomers, nor were glutamic or aspartic acids so transported; the amounts of these latter acids lost in the experiment could not be recovered as the free acids from the intestinal wall. Darlington & Quastel (72) used a similar preparation of guinea pig intestine to demonstrate the selective absorption of fructose and galactose. The absorption of fructose resulted in its conversion into glucose. Phosphate transfer did not occur. An active respiratory system was apparently concerned in the absorption of glucose; this was inhibited by O<sub>2</sub> lack, cyanide, azide, fluoroacetate, malonate and chlorbutanol (Chloretone) while the transfer by diffusion of sorbose was unaltered by these substances. 2-4-Dinitrophenol in low concentration strongly inhibited glucose absorption, constituting direct evidence for the participation of phosphorylation mechanisms in glucose absorption. Fisher & Parsons (73) found that the rate of absorption of 0.5 per cent glucose from surviving isolated rat intestine was unaffected by alteration of the

glucose concentration bathing the segments, and an accumulation of glucose occurred in the wall during the first 30 min. After this time the rate of absorption of glucose fell to a lower steady value, and this was not due to a fall in glucose concentration in the lumen. Galactose was absorbed against a concentration gradient, at a rate about half that for glucose. It, too, accumulated in the wall of the intestine. The kinetics of absorption were similar to, but not the same as those of glucose absorption. During the absorption of glucose, water accumulated in the mucosa; this was not observed during the absorption of galactose. Hestrin-Lerner & Shapiro (74) reported the interesting finding that glucose rapidly disappeared from the lumen of isolated rat intestine bathed in oxygenated saline in the absence of a concentration gradient (same fluid inside and out), but no additional glucose appeared in the outside fluid. The missing glucose could not be accounted for on the basis of combustion; when radioactive glucose was used, a radioactive substance appeared in the outside fluid equivalent to 30 to 60 per cent of the radioactivity which had disappeared from the inner fluid. The substance in the outer fluid was nonreducing and nonfermentable; its nature was not elucidated. Hetényi & Winter (75) studied the disappearance of amino acids from intestinal loops in anaesthetised rats. They found maximal absorption rates for glycine and histidine but not for glycylamide, sarcosine, and proline. Using the same technique Winter (76) showed that fluoroacetic acid introduced intraperitoneally did not alter the absorption of glucose but diminished the absorption of glycine. D'Agostino, Leadbetter & Schwartz (77) studied the ionic exchanges in saline instilled into colonic loops in dogs.  $\text{HCO}_3^-$  entered and Cl left the loop fluid in equivalent amounts, so that the total remained constant; a similar entry of K and exit of Na in equivalent amounts also occurred. Blickenstaff & Lewis (78) report the increased absorption of water and Cl from Thiry-Vella loops of small intestine in dogs after administration of atropine, due possibly to increased surface area resulting from relaxation, decreased intestinal secretion, or actual increase in gut-blood transfer; while on the other hand Cummins & Almy (79) report that in human subjects intestinal absorption of methionine and glucose (studied by the double-lumen tube method) was increased by drugs such as bethanechol (Urecholine) and eserine which increased motility and vascularity.

#### BILIARY TRACT: FAT ABSORPTION

Studies on the metabolism of the bile salts have always been impeded by the formidable nature of the chemical procedures involved in their identification and separation; but there are now appearing chromatographic methods which will undoubtedly find a ready use in the field of biliary physiology by those interested. Wootton (80), for instance, reports an elegant procedure for the quantitative separation of bile acids from ox bile by chromatography on dry silica of their methyl and acetyl esters, with identification of the compounds by means of their infrared spectra. Cook *et al.* (81) applied methods analogous to those employed in the study of renal function to the

study of bile formation in acute biliary fistula dogs. The rate of bile excretion, bile/plasma concentration ratios, and biliary clearances were determined for a variety of substances both exogenous and endogenous. Two principal factors appear to be involved in the appearance of any substance in the bile: (a) filtration through the hepatic laminae, and (b) active secretion by the hepatic cells. Selective reabsorption appears to be minimal. Water, Na, K, Cl, glucose, inulin, cholesterol, and creatinine appear to be filtered; sulfobromophthalein (Bromsulphalein), *p*-amino-hippuric acid, bilirubin, and some antibiotics appear to be actively secreted. Siperstein *et al.* (82) have provided by their studies on the fate of cholesterol labelled with  $C^{14}$  at the 4-position a picture of the major metabolic pathways of the cholesterol molecule in the body. Ingested cholesterol is absorbed almost entirely in the lymph, and for this process bile is essential. After absorption, about 80 per cent of the terminal two carbons of the isooctyl chain is oxidised, probably in the liver, appearing as  $CO_2$  in the expired air. After other minor changes, the residue is excreted in the bile in the form of bile acids. The enterohepatic circuit of the labelled bile acids is rapid, and the effective loss from this circuiting accounts for 75 to 85 per cent of the faecal steroids. The 15 to 25 per cent of cholesterol not oxidised in the liver is eliminated either through the bile or across the intestinal wall as neutral sterols containing 27 carbon atoms.

Details of the pathways and mechanisms of absorption of fats and fatty acids have been studied by several groups of workers. Bergström, Borgström & Rottenberg (83) studied the absorption and distribution of stearic acid -1- $C^{14}$  when fed to rats either incorporated into corn oil by transesterification or mixed with free fatty acids from the same source. The route of absorption was the same in either case, although absorption of fatty acid was somewhat slower probably owing to slower gastric emptying. In both cases the labelled stearic acid was rapidly incorporated into the intestinal phospholipides. Lymph glycerides were found to contain about 90 per cent of the labelled stearic acid fed, but the specific activity of the plasma glycerides remained low, indicating rapid uptake of the labelled lymph glycerides by the tissues. When labelled stearic acid was fed with corn oil glyceride or cholesterol (84) the distribution of the labelled acid between the glycerides, phospholipides, and cholesterol ester fatty acids of intestinal lymph was the same irrespective of the form in which the active stearic acid was fed (whether as free acid dissolved in corn oil, transesterified with corn oil, or as cholesterol ester dissolved in corn oil). The results are capable of explanation by either of the following hypotheses: (a) that fat is completely hydrolysed in the lumen before absorption and taken up as fatty acids, cholesterol, and glycerol, being then synthesised to glycerides, cholesterol esters, and phospholipides; or (b) that the fat is incompletely hydrolysed and absorbed partly in particulate form, in which case it must be nearly completely transesterified in the intestinal lumen or in the cells. Later, Borgström (85) showed that during the pancreatic lipolysis of glycerides in the intestinal lumen of rats



a partial resynthesis of glycerides occurred simultaneously with hydrolysis. The fatty acids liberated by lipolysis were preferentially absorbed. Diversion of bile and pancreatic juice from the intestine almost completely abolished lipolysis and resynthesis of lipides. Reiser & Williams (86) suggest that, during the absorption of fatty acids, the formation of fatty acid-dihydroxyacetone esters, with subsequent reduction and esterification, may be a normal method of triglyceride synthesis; they showed in rats that fatty acid esters of dihydroxyacetone were converted to triglycerides during absorption, only triglycerides being found in the lymph.

Reports that the administration of synthetic emulsifying agents such as the Tweens would correct fat absorption in conditions where this was defective, e.g., coeliac disease, have led to studies of the effect of these agents on fat absorption in normal subjects and animals. Tween 80 was without effect on the faecal fat excretion in bile fistula dogs (87), and several other similar agents (Tween 60, Span 60, Myrj 45) fed to rats and human subjects did not alter the absorption of fat as judged by chylomicron counts and recovery of fat in the faeces (88, 89). Apropos of these reports, it is interesting to note that according to Minard (90) Tweens 20, 60, and 80 are slowly hydrolysed by pancreatic lipase and on that account by substrate competition retard the hydrolysis of corn oil *in vitro*; this effect is however reversed by bile salts.

The demonstration by Hahn (90a) that the injection of heparin "clears" a lipaemic plasma *in vivo* although heparin has no such action when added to lipaemic plasma *in vitro* continues to stimulate studies on the nature of the mechanism involved. A synthetic fat emulsion is cleared by heparinised plasma (91) and the activity of the plasma in this respect lasts for several days at 0.5°C., but is lost in 24 hr. at body temperature. When a lipaemic plasma is "cleared" by heparin injection the fat content of the plasma does not rise as high as usual and falls faster, indicating a faster removal from the circulation (92). Swank & Levy (93) suggest that the action of heparin is to activate a "chylolytic" substance present in certain tissues, particularly those which use fat. Clearing of the plasma on heparin injection is temporary, and the tissue content of the "chylolytic" substance can be exhausted by repeated injection of heparin. Spitzer (94) finds that the "clearing factor" present in plasma is dialysable, is present in the albumin fraction of plasma, and is irreversibly inactivated by exposure to a temperature of 49°C. It is not related to serum lipase. Brown & Kauffman (95) find that the lipaemic clearing factor can be formed *in vitro* by the addition of heparin to lyophilised rat pylorus tissue.

#### GASTRIC MUCIN

The important association of the glandular mucoprotein fraction of gastric mucin with the oral activity of vitamin B<sub>12</sub> is now well recognised, and this has led to several studies of considerable interest. Glass (96) discusses the physicochemical characteristics, cellular origin, and physiological



significance of the fractions separable from gastric mucin. A scheme of chemical fractionation is described and the results compared with electrophoretic studies of gastric juice. Total gastric mucus may be considered to consist of (a) visible and (b) dissolved mucus. The former is secreted by the surface epithelial cells and dissolves to form soluble mucus which by digestion forms dissolved mucoprotease. Glandular mucoprotein is secreted by the mucoid cells of the neck of the gastric glands. Dissolved mucin, mucoprotease, and glandular mucoprotein together constitute the "dissolved" fraction of gastric mucus. Glandular mucoprotein is apparently identical with the "gastroglobulin," "mucoprotein," and "mucoid" material of other authors; the amount present in gastric juice is not related to mechanical or chemical irritation or injury but correlates well with the secretion of HCl and pepsin. Vagal stimulation and insulin injection excite its secretion. Atrophy of the fundic glands, as in pernicious anaemia (in which mucoprotease is constantly present) is associated with its absence from the gastric juice. Mack, Wolf & Stern (97), studying the electrophoretic behaviour of whole human gastric juice, confirm that "mucoprotease" and "glandular mucoprotein" exist as separate constituents of gastric juice. Both had a high negative charge; the mobility of the former was low, that of the latter high. Although the factor in gastric juice which combines with and promotes the activity of vitamin B<sub>12</sub> is undoubtedly a gastric mucin component, the exact nature of it does not seem clearly to have been established. Latner *et al.* (98) separated normal gastric juice concentrates by paper electrophoresis into several fractions, which were administered together with B<sub>12</sub> to pernicious anaemia patients. Several of the fractions separated showed B<sub>12</sub> binding capacity, and two (one from the "cathode" side, and one from the "anode" side) had intrinsic factor activity. The "anode" fraction, which was the more active of the two, contained either mucoprotein or mucopolysaccharide. Wallerstein *et al.* (99) are of the opinion that the essential role of the intrinsic factor is merely to increase the assimilation of vitamin B<sub>12</sub> rather than to potentiate its effects after absorption; the primary effect of intrinsic factor is on the intestinal wall rather than on B<sub>12</sub> itself.

Marmion and associates (100) subjected human gastric juice to the action of a mucinase derived from *Vibrio cholerae* which destroys the influenza virus receptors on erythrocytes and other cells and also inactivates gonadotrophic hormone. When the juice was then fed with vitamin B<sub>12</sub> to pernicious anaemia patients, a normal therapeutic response was obtained indicating that the intrinsic factor is not susceptible to the action of this enzyme. Chow & Yamamoto (101) purified the B<sub>12</sub>-gastric juice factor complex with the aid of Co<sup>60</sup> which was used to label the vitamin. The complex was found to have a minimum solubility at pH 3.5 to 4.0; and the molecular weight (estimated by diffusion) of a purified fraction was about  $5 \times 10^{-5}$ . However, paper chromatography showed the presence of more than one component.

Swenseid, Schapiro & Halstead (102) found that a B<sub>12</sub>-binding factor

was present in normal human duodenal secretions in about the same concentration as in gastric juice collected at the same time. In patients with achlorhydria the duodenal content of the factor was normal but the amount in gastric juice extremely low. In one case of pernicious anaemia the presence of the factor in duodenal juice could not be demonstrated. Rosenthal & Hampton (103) followed the absorption of vitamin B<sub>12</sub> from the stomach and duodenum of anaesthetised dogs. The results showed that B<sub>12</sub> absorption occurred from the duodenum and not the stomach.

#### PANCREAS

Dorchester & Haist have made a valuable study of the effect of the anterior pituitary on the intestinal content of secretin in the rat. They first (104) evolved a method of secretin assay using anaesthetised rabbits and a latin square design. Using four rabbits the expected standard error of an estimation was 10.3 per cent. The method was then used (105) to estimate the extractable secretin content of the intestine in normal and hypophysectomised rats. A reduction in secretin content was found, which was significant in terms of total activity per gm. dried intestine per unit of body weight, or relative potency. Finally (106) they showed that desiccated thyroid did not prevent a fall in the secretin content of the intestine after hypophysectomy, but that anterior pituitary extract did. A purified growth hormone fraction, and ACTH, had a similar effect. In normal rats anterior pituitary extract increased the secretin content of the intestine, but growth hormone and ACTH did not. These results indicate clearly an influence of the pituitary upon the secretin content of the small intestine, and it is to be hoped that similar studies will be made on pancreozymin and perhaps other hormones. Jordan & Hallenbeck (107) studied the effect of increased secretory pressure on the production of pancreatic juice in unanaesthetised dogs using Thomas' method of cannulation of the duodenal papilla. The maximum pressure against which the pancreas was capable of secreting was found to fluctuate from one minute to the next; arrest of the flow occurred at a pressure of 18 to 24 cm. of pancreatic juice. Increasing pressure had no significant effect on the volume-rate of secretion or the bicarbonate content of the juice until the maximal pressure was approached, when there was an abrupt fall in both. Lin & Grossman (108) determined the dose-response relationships for pancreatic enzyme output in dogs, using secretin, pancreozymin, and methacholine as stimuli. The secretion of pancreatic enzymes in response to strong stimulation was practically inexhaustible, continuing after as long as 14 hr., and indicating that even in such circumstances reformation of pancreatic enzymes kept pace with their output.

When pancreatic juice is excluded from the small intestine in dogs (109) the absorption of fat and N is variable but much less than normal. The absorption of carbohydrate is delayed, and marked splitting of fat occurs in the stomach and small intestine. The pH of the small intestine however is reported to remain within normal limits. Brooks & Thomas (110) found

ethanol, with or without 0.1 N HCl, ineffective as a stimulant of pancreatic secretion when introduced into the duodenum of dogs. The carbonic anhydrase inhibitor "6063" (see p. 162) discovered by Janowitz, Colcher & Hollander (55) was found by Birnbaum & Hollander (111) to be also effective against secretin-stimulated pancreatic secretion in dogs. The volume-rate and bicarbonate content was markedly depressed. As in the case of gastric secretion complete inhibition was never achieved. Routley *et al.* (112) described the effects of vagotomy on pancreatic secretion in dogs.

#### INTESTINAL SECRETION: COLON

Heggeness, Kirschner & Nasset (113) have reported briefly on further properties of purified enterocrinin. It is apparently a peptide containing at least six amino-acids and on injection stimulates secretion from duodenum and jejunum. It increases motor activity in the isolated guinea pig ileum. Russell & Nasset (114) also report the stimulating effect of hyperthyroidism on jejunal secretion in dogs and the depression resulting from hypothyroidism whether produced by excision or administration of thiouracil. Ethanol, administered orally or intravenously, was found by Koskowski & Mahfouz (115) to stimulate the secretion of intestinal juice in Thiry-Vella loops in the dog possibly by reason of a liberation of tissue histamine. Anthisan (2-[(2-dimethylaminoethyl)(*p*-methoxybenzyl)-amino]pyridine) prevented stimulation, and this drug also (116) antagonised the secretion produced by histamine and carbachol (carbaminoyl choline).

Klinge (117) studied the motor activity of cats colonic muscle after the removal of Auerbach's plexus, and Kern and Almy (118) described the effect of acetylcholine and methacholine on the human colon. In the great majority of cases these drugs abolished phasic contractions and caused generalised spasm and shortening.

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## BLOOD CLOTTING AND HEMOSTASIS<sup>1,2</sup>

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The two year period under review has resulted in an increasing number of papers in this field of investigation. There has been, however, considerable clarification of some areas with an appreciation of the greater complexities of the subject. In this regard, the reviews and monographs (1-38) at the beginning of the literature citations probably give a more satisfactory formulation of the individual author's views than single research papers. An important step not only for blood coagulation but for blood in general is the publication of *Standard Values for Blood* (7). Koller's listing of the blood coagulation literature each year will be found helpful (21, 22, 23). Since the last review, Wöhlisch's review (37) has become generally available. Baserga & de Nicola's book (1) is the most complete survey of the literature to date and provides a useful reference source.

During the period under review the main advances have been: (a) a clear formulation of the nature of the basic chemical reactions in blood coagulation (the conversion of fibrinogen to fibrin and prothrombin to thrombin); (b) clear demonstrations of the importance of technical details in this field and the development of more specific quantitative tests and methods; (c) a greater integration of this subject with physiology as a whole, a trend apparent in all of hematology. In this connection, one can not help observing the increasing evidence of endocrine influences in hemostasis. With improved and more specific methods, this will probably increase, since the unsatisfactory results obtained in the past were undoubtedly due to poor, unspecific methods. The review grew naturally into these three divisions. In addition there has been a clarification of several areas which were still in embryo in the previous review. Thus, a number of workers have demonstrated clearly that a material is present in plasma which under suitable conditions can be demonstrated to provide thromboplastic activity or plasma thromboplastin. There has been an increasing interest in the fibrinolytic system of the blood and an appreciation that this is not a part of the clotting system but represents rather another important physiological mechanism of hemostasis as a homeostatic physiological function. A considerable clarification has been achieved by a statement (5), made by some of the most active workers in this field, of the identity with two factors, of most of the various plasma

<sup>1</sup> The survey of the literature pertaining to this review covered the period June 30th, 1951, to June, 1953, but, as somewhat different aspects of the subject to those covered in previous recent reviews are discussed, consideration is given to recent publications outside this period pertinent to the topics.

<sup>2</sup> The preparation of this review was assisted by a grant from the P. D. Stewart Bequest of the University of Saskatchewan for stenographic help.

factors described as being involved in the physiological conversion of prothrombin. They will be referred to in this review as Ac-globulin and Factor VII, as these terms appear to be used by a greater number of workers than any of the others. Ac-globulin is used for all references to prothrombin accelerator, plasmatic cofactor, proaccelerin, Factor V, labile factor, plasma prothrombin conversion factor, and plasma accelerator globulin; while Factor VII is used for SPCA (serum prothrombin conversion accelerator) co-thromboplastin, stable prothrombin conversion factor, proconvertin, and co-Factor V. For the purposes of this review it has rarely been necessary to distinguish between the active form of these substances and a precursor form in plasma, nor did the group referred to reach agreement on this, although they all recognize it as a possibility to explain a number of phenomena. The equivalent of thromboplastin + Ac-globulin can be provided by suitable extracts of tissue (beef lung or rabbit brain) + plasma, plasma + platelets, tissue + platelets (30).

There are still many papers appearing in which no attention has been paid to the statistical evaluation of results, although in no field are there more uncontrollable variables, suggesting the importance of statistical techniques. Not only is it essential to use statistical methods for determination of significance but as emphasized by R. B. Fisher it is necessary to ask the question properly in order for the test of significance to mean anything. In this connection, the design of a controlled experiment is essential and yet is often extremely difficult in this field. One of the most important advances in the last three years may be the demonstration that "clean" syringes can be the source of such great errors as actually to be responsible for phenomena which the experimenter concludes are taking place in the circulation of the subject. One is forced to conclude that in studies of the physiology of the clotting system and clotting phenomena the only really satisfactory control on which the significance or lack of significance of the data can be established, is the control experiment using placebos prepared by someone not involved in conducting the observations and with the code only revealed after the completion of the observations and with considerable thought and ingenuity involved in the choice of suitable placebos. Certainly, the task of this reviewer would have been far less onerous if such criteria had been observed. However, as a result, the section on physiology must be read with considerable reservations, since many of the papers give insufficient data to make any evaluation of its significance and one must conclude that relatively small variations in clotting time, etc., have been so scrambled by technique that it is fortuitous that the variations are all in the direction of the variable studied. One wishes more papers included the graphic presentation in all figures, of the limits of normal as is done by MacFarlane & Biggs (39) and Roskam (12).

Reports continue to be made of coagulant and anticoagulant factors. Almost any substance will affect some clotting system, e.g., sodium chloride can be shown to be an anticoagulant. It is the observation that thromboplas-

tin and heparin are highly effective in trace quantities which is significant, together with the observation that there are large concentrations of these substances in close anatomical relation to the circulation. In this regard, the observation of Abul-Haj *et al.* (40) that hyaluronic acid is a highly effective thromboplastin in the concentrations found in tissues (actually more effective than brain thromboplastin) and therefore presumably must be physiologically significant is pertinent. One wonders how often sodium chloride, urea, hyaluronic acid, and similar commonly occurring compounds are set up as "coagulation factors". In this regard, it must be remembered that a substance usually considered of no significance in the clotting system may have important coagulant or anticoagulant properties if the base line (the clotting time) is changed by the presence of another substance (41).

No attempt will be made to cover the many reports in the past two years on the clinical use of anticoagulants and new anticoagulants now being introduced, except in so far as they illustrate points for discussion. The physiological principles involved in the use of anticoagulants has been reviewed elsewhere (19). Hemophilia was discussed in the last review so that no reference will be made to the differential diagnosis of hemorrhagic diseases, with the exception of mentioning that classical hemophilia has been divided into two and possibly three types, very similar clinically but which can be differentiated on clotting tests and specific treatment (42, 43) and that evidence is accumulating that platelet antibodies from blood transfusions may be responsible for idiopathic thrombocytopenias (44, 45). Apologies are offered to the many authors of valuable contributions reference to whom has been omitted because of lack of space.

#### THE FIBRINOGEN-FIBRIN AND PROTHROMBIN-THROMBIN REACTIONS

*Fibrinogen-fibrin.*—The past two years have seen the elucidation of the nature of the fundamental reactions of blood coagulation. This has been due to developments in protein chemistry which have provided methods for studying reactions of this complexity together with the availability of prothrombin and thrombin of sufficiently high specific activity to make the conclusions significant. Current concepts of the nature of the processes involved in the formation of the fibrin clot are largely based on the views of Flory (46) on gel formation by polymerization, as developed and applied to protein gels by Ferry (47). The assumption is made that the reactivity of a particular group is independent of the size of structure to which it is attached and that a cross-linked network of an indefinitely large size (a gel) will appear when a proportion of all the reactive groups is combined. Stimulated by these speculations a large amount of experimental information has been obtained by physical chemistry techniques which strongly favor the validity of these views. Starting with the work of Ferry & Morrison in 1947 (48) that the structure and properties of fibrin clots are greatly modified by variations of pH, ionic strength, and other factors during the clotting process, a number of investigators have extended these observations. Edsall

& Lever (49) found that the rate of clot formation increased with increasing pH from 5.8 to 7 but that the turbidity of the fully developed clot decreased, corresponding with the transition from the coarse opaque clots to the fine translucent clots previously reported by Ferry & Morrison, and various factors which markedly reduced the turbidity of the clot did not cause as marked a reduction in the yield of fibrin. Evidently structure of the fibrin can be affected without any corresponding reduction in the amount of insoluble protein at pH 6.3. Various compounds at concentrations far below those employed to produce denaturation profoundly influenced the character of the clotting process. Urea retarded clotting and decreased clot turbidity. Guanidine greatly retarded clotting but increased turbidity; formaldehyde even at low concentrations produced a marked reversible inactivation of fibrinogen, although agents inactivating sulphhydryl groups had no effect on clotting. Shulman (50) in 1951 extended the previous studies of Ferry & Shulman (51) and tested about 80 organic reagents on the clotting of fibrinogen by thrombin. Half of these delayed clotting for at least 24 hr., and the inhibition was reversible by dialysis and hence not caused by destruction of either fibrinogen or thrombin. Hexamethylene glycol, urea, and guanidine appeared to be the most effective. Shulman, Herwig & Ferry (52), in the same year, studied the influence of ionic strength and thrombin concentration on the effectiveness of these three inhibitors. The effectiveness of these inhibitors was markedly increased by increasing ionic strength and slightly decreased by increasing concentration of thrombin.

Almost immediately studies were published by Ferry, Laki and their coworkers of physical chemical studies of the clot from fibrinogen which demonstrated that by the use of these inhibitors intermediate steps could be demonstrated in the conversion of fibrinogen to fibrin. Shulman & Ferry (53) reported the results of sedimentation and viscosity studies in the presence of hexamethylene glycol at concentrations sufficient to prevent clotting indefinitely. After several hours incubation of thrombin and fibrinogen in 0.4M glycol, a more rapidly sedimenting component appeared which increased with time as the fibrinogen decreased. Laki (54) found that no clot was formed from fibrinogen and thrombin at pH 4.85 but if, after standing, the pH were suddenly adjusted to neutrality, a clot formed instantly. On taking samples of the fibrinogen-thrombin mixture at intervals, it could be seen that there was a gradual evolution of this clotting property, and they concluded that thrombin acts on fibrinogen at pH 4.85. However, Laki found that there was no change in viscosity or sedimentation rate in the system, and hence, while thrombin acts on the fibrinogen molecule under these conditions, polymerization of the product does not occur. These observations mean it is possible to identify two stages in the formation of the fibrin clot. The first stage involves the action of thrombin on fibrinogen. The second stage, the formation of the gel, does not involve the action of thrombin. Belitser & Khodorova (55) have shown that thrombin acts similarly on fibrinogen in 20 per cent urea.

Steiner & Laki (56) used light scattering to follow changes in molecular weight and particle length in the process of conversion of fibrinogen to fibrin and observed that there was initially an increase in the length of the particle followed by an increase in molecular weight. At pH 8.40, the final average length was three times that of the initial fibrinogen, and the average weight was seven times. This suggests an association of particles attached end-to-end in groups of three and two or three associated side-to-side. The end-to-end associations appeared first and appeared weaker than the side-to-side associations. The addition of small amounts of permanganate could be used to stop the formation of the gel and thus the process could be analyzed at various stages. Lowering the ionic strength of the solution caused a decrease in gelation time and a much greater increase in molecular weight. Fibrinogen can be treated with iodine under mild conditions (57, 58), and the product which can be acted on by thrombin, possesses the advantage that it is soluble in the absence of salt. Laki & Steiner (59) found the polymerization of iodo-fibrinogen by thrombin in the absence of salt proceeded to a definite molecular weight characteristic of the pH value, and this molecular weight could be reached in either direction. The particle shape was that of a very long rod. As the pH was increased, the molecular weight fell off very rapidly. Laki and Steiner concluded that the pH optimum for end-to-end association of the fibrin molecules was at pH 6, while for side-to-side association at pH 8.5.

Further light scattering studies of fibrinogen during clotting have been reported by Katz *et al.* (60, 61). They report a somewhat lower molecular weight and length for fibrinogen than previous workers, namely 340,000 and 520 Å for the rod length, 650 Å for the ellipsoid length of the fibrinogen molecules. They conclude that in hexamethylene glycol at pH 6.2 about half the protein is converted to a polymer with an average degree of polymerization of 15, a length of about 3500 Å and width double that of fibrinogen. The polymer dissociates with dilution. They postulate that the polymerization process involves lateral dimerization with partial overlapping to give a parallel end-to-end chain. Hexamethylene glycol stabilizes the polymer at an average value of 15, which corresponds to the micelle with the net free energy of association. In the absence of inhibitor, polymerization is unlimited. Similar studies on the polymer in urea have been reported by Ehrlich, Shulman & Ferry (62). Separate supporting evidence has come from flow birefringence studies (63 to 66).

With increasing knowledge of the nature of the reactions involved, direct observations of clots under the electron microscope is increasing in value. Kaesberg & Shulman (67) have observed the intermediate polymers directly in the electron microscope, using hexamethylene glycol to stop the reaction and obtain values for the dimensions of the fibrils in substantial agreement with the values obtained by flow birefringence. Steiner (68) finds that the fibrin dissolved in urea gives a typical fibrin clot after removal of the urea by dialysis. Morrison & Scudder (69) report that the mean fiber width under

the electron microscope after completion of clotting is independent of thrombin concentration, but during the course of clotting is roughly a linear function of the latter and increases steadily with time.

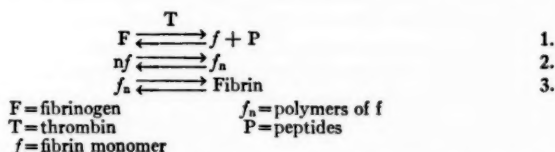
Studies of the kinetics of the action of thrombin on fibrinogen using the purified fibrinogen and thrombin preparations now available have been reported by Boyles, Ferguson & Muehlke (70), and Waugh and coauthors (71, 72, 73, 74). These studies are also important in that they are among the few in which direct determinations of fibrin have been made instead of depending upon indirect physical measurements. The limitations and assumptions involved are discussed by Waugh & Livingstone (72). A satisfactory linear relationship between thrombin concentration and rate of clotting over a wide range of values was obtained. Waugh & Livingstone plot their data in the form of the reciprocal of the fraction of total clottable nitrogen remaining in the supernatant at given time, in natural logs ( $\ln 1/\theta$ ), and obtain a linear relation for  $\ln 1/\theta$  against time. Both groups report that the kinetics follow those of a pseudo-first order. Waugh & Livingstone have investigated this anomaly. There appears to be a continuous removal of thrombin from the reaction mixture throughout the progress of the reaction, and they conclude that in addition to fibrin, fibrinogen itself removes thrombin by combining in such a way that the fibrinogen is not activated but the thrombin is prevented from activating other fibrinogen molecules.

*The action of thrombin.*—The finding of a fibrin molecule of the same size as the fibrinogen molecule and the realization that thrombin is not involved in the polymerization as described above suggest that thrombin is limited to modifying the fibrinogen molecule. While earlier workers have claimed that a denaturation of the protein occurs, the nitroprusside test distinguishes fibrin from denatured fibrinogen or denatured fibrin (75, 55). The effect of x-rays on fibrinogen solutions (76, 77) indicates that the groups necessary for clotting are not easily oxidized by OH radicals. Since the enzyme activity is not dependent on oxidation-reduction systems, it is probably hydrolytic. Guest & Ware (78) have demonstrated that purified thrombin in very high concentration lyses fibrin in as short a time as 90 min. Mihalyi (79) has shown that fibrinogen and fibrin have different isoelectric points. This suggests that thrombin acts on peptide bonds. Formaldehyde is a rapid inhibitor of the reaction at relatively low concentrations (72), and the reversibility suggests the action is on amino groups. Bailey *et al.* (80) report that whereas fibrinogen contains no terminal amino groups of glycine, considerable numbers of these groups are found in fibrin, and terminal glutamic acid residues are present in fibrinogen and not in fibrin. Lorand & Middlebrook (81) and Bettelheim & Bailey (82) show that this effect of thrombin is specific for fibrinogen. Lorand (83, 84), Laki (85), and Bettelheim & Bailey (82) by various independent methods have demonstrated that a peptide (actually two peptides) is formed during the clotting of fibrinogen. The peptide contains a number of amino acids but is highest in glutamic acid, aspartic acid, and glycine and has an isoelectric point in the region of pH 3.3.



From this data and the conditions causing dissociation of fibrin polymers, the fibrinogen molecule can be pictured (86) as having histidine residues concentrated at the ends and glutamic and aspartic acids at the center to give a negatively charged particle at pH 7. Hydrolysis of peptide bonds by thrombin results in a highly negatively charged peptide being split from the center of one side of the fibrinogen molecule, leaving a concentration of positive charges there which allows association of the fibrin molecules to a polymer (gel). The appearance of glycine in fibrin and  $\epsilon$ -lysine in the peptide as N-terminal residues indicates that thrombin attacks peptide bonds containing these.

We can now formulate the reactions taking place in the clotting of fibrinogen:



All these reactions are reversible and represent equilibria (87). The use of suitable solvents will stop the reaction at any given stage. Below pH 5 and at high ionic strength the reaction stops at stage 1. With hexamethylene glycol, it stops at stage 2. After prothrombin has acted on fibrinogen in hexamethylene glycol, dilution of the mixture causes  $f_n$  to revert to the monomer  $f$  (86). The presence of 0.002  $M$  calcium prevents this dissociation on dilution (60, 88). As would be predicted, the polymerization reaction has a negative temperature coefficient, while the enzyme catalyzed reaction shows a positive temperature coefficient (55, 79).

**Fibrin serum factor.**—Further complexity in the formation of fibrin has been reported through the work of Lorand and others. Lorand (89) in 1950 drew attention to the fact that, whereas fibrin formed by the action of thrombin and fibrinogen is soluble in a neutral urea solution, if it was allowed to clot in the presence of calcium it proved to be insoluble. In addition to calcium another factor in serum (FSF—Fibrin Stabilizing Factor) is involved. It is protein (90) and may be removed from fibrinogen by mild treatment with acid, urea, or sodium bromide reagent (91) and is not identical with any of the various factors recognized clinically. The serum factor provides a cement between the fibrin units. The solubility in urea and, in particular, in guanidine and monochloroacetic acid which are known to break hydrogen bonds, suggests that the fibrin gel is held together only by secondary forces, but evidently the plasma clot has stronger linkages, as is also shown by its higher rigidity and much slower stress relaxation (92). Edsall & Lever (93) observed that several reagents which inactivate sulphydryl groups are without observable influence on the clotting process but render fibrin clots from solutions containing calcium ions and Lorand's serum factor, soluble in urea, suggesting that sulphydryl groups are involved.



*The activation of prothrombin.*—Seegers' isolation of relatively pure prothrombin and his establishment of conditions for its activation (30) without the addition of extracts of tissue and other materials of unknown composition represents a great advance in the subject of blood coagulation. It makes possible the study of the conversion of prothrombin to thrombin by the methods of modern protein chemistry and is the realization of the hopes of fifty years of investigations on blood coagulation (Seegers, Harvey Lecture, 30). Details of the methods used are given in (29). Lamy & Waugh (94) report some physical characteristics of the purified prothrombin. The molecular weight is calculated as 62,700 with a molecular size of 119 Å long and 34 Å diameter. When purified prothrombin is dissolved in 25 per cent sodium citrate solution over a 10 to 12 hr. period, the prothrombin disappears and equivalent thrombin activity appears (95). Electrophoretically, three new components result with isoelectric points of 3.6, 4.1, and 4.7 compared to the isoelectric point of 4.2 for prothrombin itself (96, 97). One of these components has a higher electrophoretic mobility than prothrombin, while the other two have lower mobilities and thrombin activity. Their solubilities are quite different from that of prothrombin. A low molecular weight component, components of molecular weight approximately, 18,000 and 45,000 and aggregates of these are found. Waugh & Lamy (98) have identified thrombin as the fraction with a molecular weight of 40,000, hence the activation of prothrombin must be considered to be a degradation process. The reaction is autocatalytic, and the process can be initiated or accelerated by the addition of purified thrombin. Schultze & Schwick (99) have carried out a comparison of the thrombin formed from prothrombin in 25 per cent sodium citrate with that obtained with biological activators by a variety of coagulation and biological tests and conclude that it is impossible to distinguish between the thrombin formed by the two different methods.

Seegers (95) demonstrated a lag period of approximately four hr. following solution of prothrombin in sodium citrate. Thrombin activity then begins to appear and is complete in approximately 12 hr. Shortly after the start of the activation there is a decrease in the main electrophoretic peak, and at the same time the amount of thrombin recoverable from the mixture by dilution and addition of thromboplastin-Ac-globulin-calcium is considerably reduced. With the disappearance of the electrophoretic peak of prothrombin, thrombin activity begins to appear and eventually a yield of thrombin equivalent to that obtained initially by the addition of thromboplastin Ac-globulin-calcium results. These observations suggest that during the autocatalytic activation of prothrombin, an intermediate compound is obtained which is resistant to the action of thromboplastin-Ac-globulin-calcium. The use of the inhibitor, 3,4,4'-triaminodiphenyl sulfone has allowed Seegers, Andrews & McLaughry (100) to demonstrate this derivative (Prothrombin derivative I) electrophoretically. Since this refractoriness disappears before much thrombin appears, another reaction occurs (forming derivative II) before activation. Freeze-dried prothrombin may be refractory

to thromboplastin-Ac-globulin-calcium but gives complete recovery of thrombin in 25 per cent sodium citrate so that this intermediate is formed in different ways (30). McClaughry and co-workers (101, 102) report that purified prothrombin stored at  $-10^{\circ}\text{C}$ . loses appreciable activity over a few weeks and at the same time gains the ability to accelerate the conversion of prothrombin to thrombin, i.e., to cause a comparative increase in Ac-globulin activity of an activation system. They suggest that this is a property of the modified prothrombin which, while not able to act on fibrinogen, can act on prothrombin to accelerate its conversion to thrombin in the presence of other activators. Lorand, Alkjaersig & Seegers (103) report that during autocatalytic activation 40 per cent of the original nitrogen and tyrosine and 60 to 80 per cent of the carbohydrate become soluble in trichloroacetic acid and that this parallels the final yield of thrombin. The appearance of these split products does not correspond with the appearance of thrombin activity but with the disappearance of prothrombin activity, i.e., to prothrombin derivative I. When 3,4,4' triaminodiphenyl sulfone is added to the system, the carbohydrate and nitrogen are set free as before, and, as this compound evidently blocks the activation of prothrombin derivative I, the first stage of prothrombin activation is a dissociation of the prothrombin into protein and carbohydrate-tyrosine fragments. Sodium citrate and other ions in high concentration cause this dissociation, as after dialysis the carbohydrate and tyrosine residues are again precipitable by trichloroacetic acid. The second stage of activation following dissociation is due to the hydrolytic action of thrombin. Schultze & Schwick (104) find that small amounts of trypsin activate prothrombin in 50 per cent glycerol or 20 per cent albumin solutions.

The results of similar studies on the steps in the activation of prothrombin in the presence of Ac-globulin-thromboplastin-calcium will be awaited with interest. That similar steps occur in the activation of prothrombin in blood appears likely for two reasons: (a) Seegers (30) has shown that similar stages can be observed under other conditions than in 25 per cent sodium citrate; (b) the number of activators involved. Considering that the simplest combination which activates purified prothrombin is thromboplastin-Ac-globulin-calcium, this together with prothrombin makes four reactants. Reactions involving simultaneous reaction of four different molecules are highly improbable if not impossible, and in fact, are always found to consist of two or more simpler reactions. Presumably, then, the action of thromboplastin-Ac-globulin-calcium with prothrombin likewise must proceed in a series of stages. The involved schemes recently presented to show a series of cyclic reactions have ignored the possibility, which now becomes a probability, that the activators may react consecutively on prothrombin. Johnson, Smathers & Schneider (105) have already shown this for platelet Ac-globulin and its plasma cofactor. It appears to the writer that, with the large number of steps and consequent great variety of possibilities of interaction now established for the conversion of fibrinogen to fibrin and of prothrombin to thrombin, deductions from the time of appearance of fibrin in the clot

(which is the present basis of practically all studies in clotting) of the reactions of any substance or physical factor in the activation of prothrombin constitute an interesting intellectual exercise but can not be claimed to have any correspondence to reality.

#### METHODOLOGY

*Physical methods.*—Parallel with the developments increasing our knowledge of the physical characteristics of pure fibrin clots as a key to an understanding of the nature of the reaction, have proceeded other studies of physical properties, particularly of the clot as formed in plasma. These have been largely empirical with the aim of developing or understanding methods of physiological or clinical significance. Clot retraction is one of the most interesting physical properties of the fibrin clot, and the publishing of a very complete review on this subject (8) is a valuable contribution. The chief physiological factors responsible for variations in clot retraction are number of platelets, fibrinogen concentration, and blood cell mass. Increase in the latter two reduce retraction. The action of platelets depends on factors appearing during activation of prothrombin. The demonstration by Budtz-Olsen that clot retraction is not comparable to syneresis of gels and that it involves such small forces as not to be of significance *in vivo* makes necessary revision of statements in textbooks and elsewhere. Ellicott & Conley (106) and Marinkov (107) have also reported that both platelets and plasma (or serum) are necessary for clot retraction. Fantl, Ebbels & Nelson (108) tested platelet suspension after exposure to various reagents for sulphydryl groups, and, while the reagents did not interfere with the clotting of plasma by thrombin, they inhibited clot retraction completely, while the platelets still showed undiminished thromboplastin activity. Fonio & Henseler (109), have described a micromethod of measuring clot retraction for controlling anticoagulant therapy. Other studies of clot retraction have also been reported (106, 110 to 114). Morrison & Seiler (115) have studied the adhesion of fibrin clots formed from fibrinogen and thrombin and find a uniformly high adhesion of the clots to all surfaces except silicone. The adhesive force observed (*ca.* 1 gm. per cm<sup>2</sup>), while small compared to ordinary adhesives, when calculated to physiological terms is quite adequate for hemostatic function.

A few reports have appeared of methods which involve a continuous or semicontinuous recording of changes in blood or plasma occurring during clotting. When one compares the reviews of this subject with those of other subjects in physiology appearing in these volumes, one can not help being struck by the apparent neglect by the workers in this field, of the great developments in instrumentology and the thought that we are missing much of physiological significance through not having such instruments. In devising such instruments, however, workers appear to assume that the use of a physical measurement will control the main variables in clotting which occur in the circulation and in drawing the blood sample. Thus, Haley & Stolarsky

(116), using electrolytic resistance measurements in a Lucite cell, claim that their automatic recording apparatus gives a more accurate measurement of the events occurring during blood coagulation because the values from resistance measurements were "consistently higher," than those obtained by visual inspection. This is both a *non sequitur* and not confirmed by the data. Their data suggests that it sometimes takes longer for a volume of blood to clot in a lucite vessel than a single drop on a lucite slide, and as the standard error of the mean fibrin appearance time measured in a cell was identical with the standard error of the mean fibrin appearance time on the slide, the accuracy of the two methods is the same. Several of the instruments devised provide for the examination of only one or two samples at a time and have no temperature control. Unless a number of blood samples can be followed simultaneously the instrument is of very limited value, while control of temperature and cleaning of cells used are essential points of technique which must be investigated in developing the method. A number of other methods of measuring clotting of whole blood based on photokymographic recording have been described which depend on changes in blood viscosity (117, 118) elasticity (119, 120), electrolytic resistance (121), and optical density or turbidity for whole blood (122, 123), for plasma (124 to 129), and for prothrombin time (130, 131). Quivy & Bertrand (132, 133, 134) use the change in optical density to measure various activators and inhibitors of clotting of plasma, and, by converting the data with probits to straight lines, several inhibitors or activators can be studied simultaneously for mutual interaction, whereas such data is not amenable to analysis by other means. Green (135) uses optical measurements to determine fibrin strand size in plasma clots. Burstein & Lewi (136) report that the species specificity of fibrinogen may be demonstrated by physical means as well as immunological, but the effect observed may be due to variations in Lorand's factor.

*Coagulation tests and methods.*—Various authors write unfavorably of whole blood clotting times. This seems rather unjustified. All methods for the determination of the clotting time require skill which can only be obtained by practice, and the final criteria of all methods should be the value of the results obtained, when used by investigators who have actually mastered the technique, together with the standard error of the method as reported by such investigators. In any case the technique of taking the blood sample is probably the most important factor of all. An excellent demonstration that the accuracy of results obtained in determining clotting times depends more upon trained subjects and trained observers than on any mechanical means of measurement is provided by Pichotka & Reichel (137). They use a slight modification of the capillary tube method, in which the capillary tube is sealed directly into 22 gauge hypodermic needles in the centre of the connecting cone with paraffin. The mean clotting times of individual rabbits ranged from 180 to 220 sec. with standard errors of the mean of 3 to 7 sec. The average of the whole group was  $200 \pm 2$  sec. Such results were obtained after three weeks of training of the animals. Excitement

of the animal, unskilled sampling, or deliberate injury as by pricking with the needle or pinching a forefoot with forceps resulted in reducing the clotting to about half (about 100 sec.). Similar emphasis on the significance of training of operator and subject is indicated by Allen *et al.* (138). Macht & Hoffmaster (139) have modified the Lee and White technique to control the angle of tilt: the tube can be tilted before the surface film of blood is broken. Copley (140) describes a slight modification of the needles to make possible an indwelling needle for blood samples for coagulation studies.

A point frequently overlooked and responsible for unreproducible results in this field is the problem of cleaning glassware before and after use (5, p. 157). A very significant observation in this regard is the report by Tulloch, Overman & Wright (141). They compared times obtained when each blood sample was taken with a separate glass syringe presterilized by heat, with the values for samples taken successively with the same glass syringe washed with water and saline between each venipuncture. They find that when one syringe is reused for successive venipunctures, the blood clotting time is accelerated. The presence of thrombin activity in the syringe can be demonstrated by washing the "washed" syringe with fibrinogen solution. The fibrinogen clots. Again, this illustrates that the syringe used is as important a part of the method of measurement of clotting time as the test tube in which the final endpoint is read. The importance of the glass surface is also brought out by observations of Foster (142) on the assay of heparin with plasma, in which cleaned and stored pyrex tubes give very irregular end-point responses, while satisfactory results are obtained with freshly cleaned pyrex glass tubes, silicone-coated glass tubes, or cellulose-nitrate tubes. The absorption of thrombin on the glass walls of test tubes as a source of error is also emphasized by Quick & Hussey (143). Lehmann (144) indicates the importance of checking the detergents used, as the ionic detergents, chiefly alkylsulphates, bind calcium, and sufficient can be left on the glassware to interfere seriously with the prothrombin time. Nonionic detergents do not interfere in this way. Lovelock & Porterfield (145) find that the concentration of calcium required to produce clotting varies markedly with the ionic strength of the plasma. At low ionic strength very small amounts of calcium (0.08 mM) are effective in causing clotting, and this amount of calcium may be leached out of the glass container.

The use of silicone has become standard procedure in this field, and with the wider spectrum of silicone plastics available it is possible to adapt this to all types of equipment, even on a plant scale (6, 146). Tullis & Rochow (147) describe the various techniques and applications available. Brambel (148) has shown that silicone coatings are not interchangeable as although all the plastics tried were nonwetttable for water, only drifilm showed non-wettability for blood and gave complete recovery of platelets. Evidently, other factors than water-wettability are involved in the effectiveness of drifilm. Lovelock & Porterfield (149) suggest that electrostatic charge is the significant factor. The observation of Sawyer & Pate (150) that thrombo-

sis occurs when there is an electrostatic potential difference between the area under observation and elsewhere in the vessel may be a fundamental one of great importance for both *in vitro* and *in vivo* studies of blood coagulation. The zeta-potential is another possible factor (151). The equally great importance of surfaces for experiments *in vivo* is emphasized by the report of Nolf & Adant (152). Methods are now available for obtaining platelet concentrates for study and transfusions (44, 153, 154, 155, 156). Methods for platelets counts have been surveyed by Brecher & Cronkite (157), and Horanyi & Zadory (158) describe a resistance test for platelets. The remarks made concerning the necessity for technical skill combined with a quantitative estimate of the biological variation apply equally well to the bleeding time. The reader is referred to Roskam (12) for a description of such methods. Several other methods are described for measurement of bleeding and hence, by inference, the vascular and platelet factors in hemostasis [Copley & Chambers (159), Copley & Kozam (160)]. Correll *et al.* (161) have developed a standard bleeding test in rats for serotonin which may have wider application.

A very useful summary of the various "prothrombin" tests is the little monograph by Biggs (9a) which, together with the summary by Alexander (162), provides a useful introduction to the subject. It is now generally appreciated that these are not methods for the estimation of prothrombin in a chemical sense but empirical tests which detect variations in the rate of appearance of detectable amounts of thrombin under certain conditions. Like the clotting time, they are of real value empirically in reflecting changes in hemostatic mechanisms, and, in fact, the one-stage methods are essentially modifications of the classical determination of clotting time to detect changes not reflected in the ordinary clotting time. The reverse is also true. For purified prothrombin, it is possible to measure this accurately after activation to thrombin against a standard fibrinogen. Although this is the two-stage principle, it is well to understand that there are really two separate procedures: the assay of purified prothrombin in which it is activated in a suitable system and the thrombin formed measured against standard fibrinogen solution, and the two-stage test applied to plasma. The latter is referred to in this review as the two-stage prothrombin time and will be spoken of as a time, i.e., an increase in the value represents hypocoagulability. As discussed later, the same problem in definitions occurs with heparin. As controls for prothrombin time determinations, Davis & Elert (163) advocate the use of normal plasma, flash-frozen, sealed and stored in the deep-freeze. Most workers now agree that prothrombin times should be expressed in seconds and not as a hypothetical per cent of normal [Shapiro & Weiner (164)]. Minor changes in detail of the test are described (165). Reports (166 to 170) continue on micromethods and capillary techniques for use at the bedside and with small animals. In this connection Montigel (166) emphasizes the significance of temperature control. Volk & Losner (175) and Confortini & Degradi (171) use photoelectric instruments for determining



the end-point. A new, simple, and rather ingenious approach is offered by Marbet & Winterstein (172, 173) in which plasma, etc., is mixed in the chamber of a 2 cc. record syringe and the dropping of blood or plasma from the needle observed. The same sample and set-up can be used for determining heparin by using sufficient thrombin to give a clotting time of 10 sec., and they describe a coagulation set which gives a convenient means of following prothrombin time, antithrombin time, Lee and White, and the Howell clotting times. Lewitus (174) compared the prothrombin time and the Halse coagulation time for patients on dicumarol and observed that the shortest coagulation time corresponds to an activity of 50 per cent by the prothrombin time and suggest that this is a factor in developing intravascular thrombosis. Volk & Losner (175) again emphasize the importance of the concentration of the anticoagulant solution and its accurate measurement if erroneous estimations of prothrombin time are not to occur. They (176) use the prolonged clotting time resulting from the addition of suboptimal amounts of sodium citrate to detect small decreases in prothrombin activity. Studies are reported of factors in the one-stage prothrombin (177) and two-stage tests (178, 179, 180).

A number of publications deal with the other component of the prothrombin time test, thromboplastin (Quick & Hussey, 181). Modifications in its preparation and storage are described, including the testing of commercial preparations (182 to 188). Biggs (9a) emphasizes that when introducing new thromboplastins, in addition to comparing the effect these have on the prothrombin time in the normal and diluted plasma, it is necessary to have clinical records on anticoagulants to determine the values of the prothrombin time resulting in hemorrhage, and Bronstein (189) also discusses the difficulty of standardizing different thromboplastin preparations in terms of each other. Thromboplastic activity of various tissue extracts and phospholipids is reported by Blaustein, Huber & Alberian (190), Kahnt (191), and Hecht and co-workers (192 to 195). Bertrand & Quivy (133, 196, 197) have demonstrated that brain thromboplastin and snake venom (*Bothrops Atrox*) act independently of each other, thus explaining an apparent synergism. Burstein (198, 199) has compared the effects of thromboplastin prepared from rabbit and goose brain on the prothrombin time of various species and finds that the species effect can be corrected by the addition of serum from the same species as the thromboplastin, as does Mann & Hurn (201) for mammalian species. Various methods have been proposed for stabilizing thromboplastin in [hydroquinone (202), urea (203)]. Hartmann (204) reports an inhibitory effect of certain thromboplastin preparations on thrombin, and Schmid (205) removes inhibitors in brain thromboplastin by addition of toluidine blue and incubation. The inactivation of thromboplastin by cobra venom is not due to lecithinase A, (206, 207).

By modification of the test, the prothrombin time can be made fairly specific for various factors in plasma and tissues. In fact, pending the isolation and resulting chemical definition of these factors, the latter can only be



defined in terms of activities in such systems. About the first of such modified tests was Owren's one-stage prothrombin time (the p and p method) (208 to 211), in which the diluted plasma sample is mixed with beef plasma filtered through 50 per cent asbestos filter pads, together with the thromboplastin and calcium. This method is sensitive to changes in prothrombin and Factor VII only. Ware & Stragnell (212) have recently described a similar method. The only routine method for the determination of prothrombin which utilizes fractionation of the plasma proteins before the determination is that of Shinowara (213). Modifications in testing for Ac-globulin are described by Olwin (214) and Wolf (215), for Factor VII by Stefanini *et al.* (216), and for prothrombin by Owren (211). Biggs & Douglas (217) discuss testing plasma for prothrombin in plasma. They conclude the most reliable method is the two-stage procedure carried out on *undiluted* plasma without the addition of activators other than brain thromboplastin and calcium, in which the rapid evolution and neutralization of the thrombin is followed. Some progress has been made in methods for the isolation of these factors by Koller and co-workers (218 to 221) and Milstone (222).

One of the definite advances in the two-year period is the demonstration, with the development of specific tests for it, of the presence of material in plasma which under suitable conditions can act as thromboplastin. In this regard, the prothrombin consumption test first described by Brinkhous in 1939 (223) has become a valuable tool. It may be pointed out that nothing can be more artificial than this test which follows the level of prothrombin in the blood after clotting has taken place and involves concentrations a hundred-fold of those acting in the original clotting process, and yet this artificial test is yielding a new insight into the latter process as well as into factors significant in hemostasis. The prothrombin consumption test can be used either as a test for thromboplastin as used by Campbell & Stefanini (224) with native platelet-free human plasma, or as a test for the factors involved in the development of thromboplastin activity in plasma (225). As shown by previous investigators, platelets do not provide thromboplastin but do provide activity equivalent to Ac-globulin (105, 226). Details of the test have been studied and improvements reported (227 to 230). Demonstrations and methods for plasma thromboplastin based on other principles have been reported by a number of workers (39, 202, 231 to 236). Other studies on plasma thromboplastin have been reported (222, 224, 237 to 242).

*Chemical methods.*—A new chelating agent, ethylenediamine tetracetic acid (EDTA), forms unusually stable complexes with the alkaline earths and heavy metals (243) and is an excellent decalcifying agent, ten times more effective than sodium citrate (244). Proescher (245) and Hadley & Larson (246) report satisfactory experience with it as a general anticoagulant, and Dillard, Brecher & Cronkite (247) for successful platelet transfusions. Equally useful for many investigators is its application in a new method for direct titration of calcium in blood serum described by Holtz & Seekles (248). A review by Thunberg (249) of the occurrence of citric acid in the animal

organism is useful in giving variations in citric acid levels of blood under various conditions.

It is remarkable that the large body of knowledge that has been obtained regarding blood coagulation is based almost entirely on one simple little test: the timing of the formation of a fibrin clot. Several recent reports suggest that other tests may be developed for the enzyme, thrombin (250, 251). Sternberger (252, 253) has developed a test for preformed thrombin present in the circulation and reports being able to demonstrate the presence of thrombin in the circulation of normal persons, suggesting continuous activation of prothrombin *in vivo*.

There is a continuous series of reports of methods and modifications of methods for determining fibrinogen in blood. At the same time that some are striving for greater accuracy, the increasing appreciation that fibrinolysis occurs clinically is increasing the need for qualitative methods for the rapid estimation of plasma fibrinogen concentration. Schneider (254) describes a rapid method based on the dilution which will still give a visible clot. Smith, Rosenfeld & Shinowara (255) have studied the  $\beta$ -naphthol reaction of Lyons and show that this is simply a qualitative expression of the level of the fibrinogen concentration in the blood and does not represent a different fibrinogen. Other indirect methods for fibrinogen are described (128, 256 to 259). Direct determination of fibrinogen requires its separation from plasma either as fibrin or by precipitation with salt (260, 261, 262) or alcohol (263), followed by gravimetric or colorimetric measurement. Fearnley (264) indicates that contamination of the clot with other proteins (a problem overlooked by Ingram, 265) is due to occlusion rather than to absorption and can be avoided by a sufficiently high speed of centrifugation. A useful method for many investigators will be the method of Ratnoff & Menzie (266) for the determination of fibrinogen in small samples of blood (0.1 ml.).

Most studies of vitamin K have been indirect, deducing its action and factors affecting it from changes in prothrombin time. The use of direct methods for the determination of vitamin K would add much more regarding its significance in physiology. The basic method for measuring vitamin K is the biological assay on the chick. Dam, Kruse & Sondergaard (267) have reported various improvements. Colorimetric methods for the vitamin are described (268, 269). A more sensitive method might be polarographic, judging from the reports of Forjaz (270), Maruyama (271), and Knobloch (272, 273). The radioactive tracer technique avoids some difficulties. Phillips *et al.* (274) report the preparation of 2-methyl- $C^{14}$ -1:4 naphthoquinone ( $K_2$ ) and Lee *et al.* (275) of 2-methyl- $C^{14}$ -3-phytyl-1:4 naphthoquinone ( $K_1$ ). Even with labelled vitamin, it is difficult to detect the traces of the vitamin which are presumably responsible for activity. Most investigations on vitamin K have used menadione ( $K_3$ ) and related compounds, and only recently  $K_1$ . Baumgartel & Zahn (276) describe a synthesis of  $K_2$  (2-methyl,3-difarnesyl, 1, 4-naphthoquinone), using a culture of *Escherichia coli*.

**Heparin.**—Methods for determining heparin in blood and tissues have

been recently reviewed by Jaques (277). Judging by number of publications, interest is chiefly being taken in the blood, although there are large quantities of heparin in tissues and only rarely is there any quantity of heparin in blood. Since the heparins in different species have different specific biological activities, the use of beef heparin as a reference standard can be quite misleading when applied to other species; it is necessary to isolate heparin from the species studied. A routine laboratory method for heparin in tissue is needed. Studies on extraction procedures are reported by Jones *et al.* (278), Kimura (279), and Utsushi (280). Several methods of assay have been described for heparin (142, 281, 282, 283). Marbet & Winterstein (284) have compared the effect of various heparins and sulfated polysaccharides on the clotting of plasma with thromboplastin, calcium chloride (prothrombin time) and with thrombin (antithrombin time). Various thromboplastins vary in their ability to neutralize heparin, and this is not related to thromboplastic activity. Likewise the heparins vary in their antithromboplastic activity, and this does not parallel the antithrombic activity. In particular the beta heparins show a considerably lower antithromboplastic activity compared to antithrombic activity. Marbet & Winterstein also comment on the difficulty of comparing the different heparins and particularly synthetic anticoagulants since the relationships between concentration and clotting time are not parallel.

Metachromasia is one of the most useful properties of heparin, since it can be used both chemically and histologically to identify heparin and related compounds. Metachromasia refers to the property of heparin and other high molecular weight acids to cause the appearance of a new absorption band at a shorter wave length, when added to dilute solutions of certain basic dyes such as toluidine blue and Azure A at a pH between 3 and 9.5. To the eye, the blue colour of these particular dyes shifts to a reddish purple. With high concentrations of acid the metachromasia is reversed (285). Ball & Jackson (286) have examined commercial batches of toluidine blue chromatographically since many dye samples are poorly metachromatic. Chromatographic fractionation by this technique might well be adopted by users of toluidine blue, although in our experience it is not necessary if biologically standardized Azure A is used, since this is chromatographically a single dye. They also report that the metachromatic absorption bands of toluidine blue and Azure A are not identical. Metachromasia with toluidine blue is not absolutely specific for  $\text{ROS}_2\text{H}$  groups (285, 287). Nucleic acids will cause metachromasia (285, 288, 289), while many substances (e.g. streptomycin, 290) are antimetachromatic.

The determination of heparin in blood requires the separation of the heparin from the blood proteins followed by its measurement. Gibson *et al.* (291) and Bassiouni (292) have modified the method of Jaques, Monkhouse & Stewart (293) for the precipitation of heparin from plasma. However, modifications do not measure the metachromatic material in blood but the amount of dye-precipitating material. The methods are evidently satis-

factory for following injected heparin but lack specificity giving a very high blank value (2 mg. per 100 ml. for Bassiouni). This is not surprising since proteins will precipitate the dye, and, in fact, toluidine blue has recently been suggested as a precipitant for plasma proteins (294).

Various coagulation tests for heparin have been described. That chiefly used is the protamine titration, which is applied to incoagulable or hypo-coagulable blood and requires the determination of the exact amount of protamine to reduce the clotting time to normal values. The amount of heparin equivalent to the amount of protamine required to obtain a normal clotting time may be readily calculated by standardizing the protamine sample used with commercial heparin. In practice the subject must have a clotting time of at least twice the normal value, and the addition of graded amounts of protamine should show reduction of the clotting time to normal values in one or more tubes. Equivalent heparin should either be isolated under the general conditions of the experiment, or it should be demonstrated that an equivalent amount of heparin from the particular species gives prolonged clotting times of the order found. Failure to observe such criteria has resulted in reports in the literature of amounts of heparin in the blood equivalent to 10 per cent of the animal's weight, yet heparin is a trace substance in the body.

Protamine is also used as an empirical coagulation test, the protamine index of Allen (295), in which the amount of protamine required to shorten the normal clotting time is determined. The basis of the test is not understood, but it is of considerable empirical value. It would save much confusion if the results from these two tests, the protamine titration and protamine index, were kept distinct. Nikkilä & Majanen (296) point out that the final outcome of the protamine index is mainly due to substances which both influence blood coagulation and combine with protamine to form compounds inactive in the coagulation process. Chemically most of these substances are polysaccharides and will include, apart from heparin itself, the phosphotungstic acid-precipitable mucoprotein fraction of serum. Using figures in the literature, Nikkilä & Majanen calculate that the heparin present in normal blood binds about 0.2  $\mu$ g. protamine per ml. and that only 1 per cent of the anticoagulant activity of blood can be due to heparin. The remainder is due to mucoprotein, and, while a 0.75-fold change in mucoprotein concentration will change the protamine index by one step, it will require a hundred-fold change in heparin concentration to change the index by one step. The latter corresponds to the injection of about 100 mg. of heparin in a man of average weight, which will significantly lengthen the clotting time. Nikkilä & Majanen point out that a weakness in this argument is that heparin may be included in the phosphotungstic acid-precipitated mucoprotein fraction of serum, but the author has observed that heparin is not precipitated with the plasma or serum proteins by trichloroacetic acid and hence will probably not be precipitated by phosphotungstic acid. A modification of the protamine test using the silicone technique is described by Morrice,

Drake & Goodrich (297). An equal volume of protamine and blood is taken (298). The glucose tolerance test causes a slight rise and the injection of epinephrine a fall in the protamine index. Many workers, e.g., Meneghini & Cervini (299) use toluidine blue in place of protamine. The Gerendas' test is one of the more sensitive tests for heparin (300), but Monkhouse *et al.* (301) have shown that, when applied directly to serum or defibrinated plasma, it shows no correlation with the actual heparin present. Marbet & Winterstein's antithrombin time (172) gives a method of following heparin injections which should be of real value in physiological and clinical investigations because of its speed. Heparin may be removed from plasma by absorption on calcium phosphate (302) to differentiate it from antithrombin. In general, it may be said that satisfactory methods are now available for measurement or recovery of added heparin from blood when added in considerable amounts. The same methods are satisfactory for the recovery of native heparin from blood when present in considerable amounts. However, these methods are not so specific that one can use them to conclude that material recovered by them from normal blood is heparin. Winterstein & Marbet (303) describes a nephelometric method for determination of excreted heparin and uroheparin in urine using dimethyl-amino-methyl-dibenzofuran and describe a semiquantitative bedside test for this. The new histological methods are discussed later, but reference should be made to the announcement of a simple direct method (304) for absolute basophil leucocyte counts which should result in an increase of our scanty knowledge of these cells and possible relationship to heparin.

#### PHYSIOLOGY

*Prothrombin and vitamin K.*—Most of the studies to date have used the one-stage (sometimes the unmodified two-stage) prothrombin time, and therefore the results described may be due to changes in prothrombin or Ac-globulin or Factor VII or changes in several of these substances. In general, these substances appear to be influenced by the same factors influencing the liver although Factor VII seems to be most sensitive, Ac-globulin next, and prothrombin least, so that Factor VII levels respond first to Vitamin K lack and to dicumarol drugs and are more commonly responsible for variations in prothrombin time (18, 217, 305, 306). There are probably qualitative differences in the nature of the deficiency of coagulation factors in different species, since while Dam (17) originally showed that, in the chick, plasma from dicumarolized birds shortens the prothrombin time of plasmas from the vitamin K-deficient, and vice versa, Quick, Hussey & Collentine (307) do not observe this in the dog. A series of interesting papers have been published by Rice, Boulanger & Plummer in which they investigate the question of the relationship of complement and coagulation in guinea-pigs by studying the variation in both systems with various dietary and other agents (308 to 312). Scurvy causes no change; low-protein diet gives increased prothrombin times. Chloroform causes a decline in coagulation

factors, but complement titers are less affected, while gum acacia affects complement more than coagulation. Ethionine and carbon tetrachloride causes a marked fall in Ac-globulin, fibrinogen, prothrombin and complement components, and choline or methionine will not correct this, although they ameliorate the fatty liver. Solvonuk *et al.* (313) have used  $^{14}\text{C}$ -menadione. The radioactivity disappeared rapidly from the site of injection and likewise very rapidly from the blood, appearing in the urine. No fixation of the activity in any tissue or blood was observed, in marked contrast to the results obtained in the same laboratory with  $^{14}\text{C}$ -dicumarol, which was fixed in the liver. The rapidity of excretion is remarkable. Neukomm *et al.* (314) have injected 2, methyl, 1,4-naphthyl hydroquinone  $^{32}\text{P}$ -diphosphoric acid into rats. In some tissues, the exchange of  $^{32}\text{P}$  proceeded more rapidly than *in vitro*. While it has been taught almost universally for nearly 20 yr. that bile is necessary for the absorption of Vitamin K from the gut, this view is challenged by Fantl, Nelson & Lincoln (315), who report that production of biliary obstruction does not abolish urinary excretion of the drug on oral administration. They describe a K-vitamin saturation test. Witte (316) concludes that as Vitamin K in some cases of hepatitis causes improvement, impaired absorption of K from the intestine may be a factor in the fall of prothrombin and Ac-globulin.

It has been generally accepted that  $\text{K}_1$  (2 methyl, 3 phytol, 1,4 naphthoquinone) and  $\text{K}_3$  (2 methyl, 1,4 naphthoquinone) are interchangeable. However, a number of clinical reports have recently established that  $\text{K}_1$  rapidly and completely normalizes the prolonged prothrombin time following dicumarol, while the effect of the same or larger doses of  $\text{K}_3$  is much slower and never as complete (3, 5, 317, 318). Other differences have been demonstrated. Quick & Collentine (319) have shown that the Vitamin  $\text{K}_1$  is much more effective on the prothrombin time response of cholecystonephrostomized dogs, and Ley *et al.* (320) have shown  $\text{K}_1$  but not  $\text{K}_3$ , successfully restored the prothrombin time to normal in two cases of idiopathic hypoprothrombinemia characterized by an almost complete lack of prothrombin without decrease in activator factors. Differences have been found even in the chick assay (321, 322).

Further information has been obtained on hepatic factors and prothrombin (323). Frank, Frank & Fine (324) have studied plasma prothrombin activity by the one-stage prothrombin time in hemorrhagic shock in the dog. They report a reduction of prothrombin activity which is not related to the duration of hypotension but exhibits a striking relation to the degree of progressive circulatory decompensation. Hypotension of even very short duration markedly delayed the recovery of prothrombin activity depressed with bishydroxycoumarin [dicumarol; 3,3'-methylenbis(4-hydroxycoumarin)]. Selenium causes a rise in prothrombin time (325). Field, Graf & Link (326) report that with the hypoprothrombinemia and lowered fibrinogen level developed in dogs on chloroform, the purine bases markedly reduce the hypoprothrombinemia and protect against a reduction in plasma fibrino-



gen. As creatine gives some protection against hypoprothrombinemia without preventing plasma fibrinogen reduction, they conclude that prothrombin synthesis by the liver can be affected independently of other normal functions. Owren (211) reports that the hypoprothrombinemia and anemia of macrocytic anemias are corrected by a protein synthesis factor. Della Santa & von Kaulla (327) confirm the results of previous workers that an increased prothrombin time can be produced in subjects with hepatic disease by doses of bishydroxycoumarin, etc., ineffective in the normal individual, and suggest this as a test to measure "the prothrombogenic function" of the liver quantitatively. One could equally say that it measures the detoxicating power of the liver for the prothrombopenic agent. Spinks & Jaques (328) have reported further data to show that the prothrombin time following bishydroxycoumarin is directly related to the time the drug remains fixed in the liver. Bishydroxycoumarin labelled in the coumarin ring with  $C_{14}$  gave similar results to that labelled in the methylene bridge (329). Jürgens (330) challenges present views on the role of the liver, as he reports that Vitamin  $K_1$  administered to rabbits on hepatotoxins and to hepatectomized cats causes the almost immediate normalization of the prolonged prothrombin time and activator factors due to previous dicumarol. This can only be reconciled with the equally direct experiments of Lupton (331) and others by assuming both hepatic and extra-hepatic formation of prothrombin and activator factors, as also for the action of vitamin K.

Factors in the intestinal synthesis of Vitamin K are demonstrated by Matoth (332). Two monographs have been published on prothrombin in the newborn and treatment with Vitamin K (9, 10). Larsen shows that the lower prothrombin activity normally present immediately after birth is not influenced by Vitamin K treatment of the mother *ante partum* and therefore the relatively low prothrombin activity at birth cannot be due to Vitamin K deficiency. It is the fall of prothrombin activity which occurs in the first day *post partum* that is prevented by treatment with Vitamin K. Plum (333) reports that the prothrombin content of infant blood shows no seasonal variation, and from the age of three months most of the values are within the normal range for older children and adults. The decrease is in both Factor VII and prothrombin (334). The prothrombin time of newborn dog pups and lambs has been studied by Field, Spero & Link (335). Low levels of plasma fibrinogen occurred at birth, but normal adult levels were attained at 24 hr. (dog) and 72 hr. (lamb), while the diluted one-stage prothrombin time was prolonged at birth but reached normal values in 48 hr. (dog) and 72 hr. (sheep). They conclude the low fibrinogen at birth is indicative of depressed hepatic function and the low prothrombin is probably of the same origin. In addition it is probable that Vitamin K is not readily transmitted across the placenta of the sheep and dog. Bori & Papio (336) report that colostrum contains a considerable amount of thromboplastin and some prothrombin. Evidently "prothrombin" production is limited by factors not yet known, since, in the newborn, prothrombin production is limited to a



relatively low level not initially due to Vitamin K deficiencies, while in the normal adult, prothrombin factors appear relatively constant yet are increased in pregnancy. The thyroid may be one factor (337, 338, 339). Various effects of injections of Vitamin K on liver functions have been observed (340 to 347). These are probably nonspecific and may be due to stimulation of adrenal cortex by pharmacological doses (348).

*Fibrinogen.*—Fibrinogen is the most labile of the plasma proteins. The turnover rate of fibrinogen in the normal intact animal using  $S_M$  has been determined by Madden & Gould (349) as 6.0 days (dogs) and 8.1 days (human). While this is a faster rate than that for any of the major plasma proteins, it is slower than would be expected from studies on hepatectomized defibrinated animals, which suggests the latter represents a major call on fibrinogen production. Frank, Frank & Fine (350) report that hemorrhagic shock in the dog does not cause any change in plasma fibrinogen concentration other than that due to hemodilution or transfusion. In parallel experiments, they defibrinated their animals by intravascular administration of thrombin. The regeneration of plasma fibrinogen in normal dogs was rapid, but it did not occur in the hypotensive phase of hemorrhagic shock or in post transfusion of irreversible hemorrhagic shock and was markedly delayed following a brief period of reversible hemorrhagic shock. Evidently, fibrinogen synthesis is also affected by hepatic anoxia. Many observers have reported that ACTH and cortisone cause a fall in erythrocyte sedimentation rate in rheumatoid patients and a fall in plasma fibrinogen levels (e.g. 351, 352). Vaughan (351) suggests it is due to the direct action of corticosteroids in the manufacture of proteins. Fearnley & Bunim (353) have shown that ACTH will cause a marked fall in plasma fibrinogen in some normal individuals. Henriques, Henriques & Selye (354) in 1949 reported that rats fasted for 24 hr. and exposed to cold showed a fall in the plasma fibrinogen. As tissue damage causes a rise in plasma fibrinogen, this observation is surprising, since the rats showed a high incidence of severe gastric ulcers. Simultaneous exposure to cold and fasting reduces the rise in plasma fibrinogen after trauma (355), and total adrenalectomy greatly decreases but does not abolish it, whereas it is not affected in the adrenal demedullated, sham-operated normal rat (356). This suggests the adrenals play an important role in the fibrinogen response, probably through protein metabolism (355). Adrenalectomy had no effect on the level of plasma fibrinogen or its rise when monkeys were made scorbutic (357). Rhythmic variations of as much as 100 per cent in the plasma fibrinogen concentration during the menstrual cycle are reported by Cohen & Berk (358) for the baboon, and they suggest that fibrinogen level is affected by the ovarian hormones. Campbell, Lei & Davidson (359) report a very pronounced increase in plasma fibrinogen when diabetes is produced in dogs with purified growth hormone.

*Thromboplastin.*—Reference has already been made to the important observation of Abul-Haj (40) that hyaluronic acid has a higher thromboplastic activity in the one-stage prothrombin time and on the clotting time

of whole blood than human brain thromboplastin. Fiala, Meranze & Roth (360) report that incubation of plasma with hyaluronidase results in loss of coagulability on recalcification, and for platelets, loss of their clot-accelerating activity. They suggest that the effect on thromboplastic activity is not due to hydrolytic action of hyaluronidase on thromboplastin but represents a competitive inhibition. Stoner & Green (361) have continued studies of the coagulation factor in muscle ischaemia.

*Heparin*.—A useful short review which summarizes the position of heparin among the mucopolysaccharides has been published by Marbet & Winterstein (362). The review by Jaques (20) discusses the physiology and pathology of heparin, while a general review has been provided by Salvini (27). A development of importance for future studies on the physiology of heparin is Jorpes' isolation from crude heparin of a heparin monosulfuric acid which can be oxidized with periodic acid and then reacts with Schiff reagent, and his demonstration that this reaction is given by the mast cells. This makes it possible to distinguish histologically between heparin and heparin monosulfuric acid which is presumably the building-stone for the more highly sulfurated compound (363, 364). Marbet & Winterstein (365) have isolated from beef and sheep lung a new type of heparin,  $\beta$ -heparin (monosulfuric acid), in which the amino sugar is galactosamine instead of glucosamine. They state that sulfonation of  $\beta$ -heparin gives a mucioitin trisulfuric acid ester with higher anticoagulant activity than beef  $\alpha$ -heparin. Heparins with anticoagulant activity have been isolated by Smith *et al.* (366) from hog gastric mucin, by Veil & Quivy (367) from the scales of carp, *Cyprinus carpio*, and by Frommhagen *et al.* (368) from sea clams. The last showed actually higher anticoagulant activity than beef heparin, particularly *in vivo*. Sylvén *et al.* (369, 370, 371) report the separation from ox liver capsules of a heparin-lipoprotein complex. The lipoprotein has the same physical, chemical, and biological characteristics as the heparin-complement of serum and therefore they suggest that the heparin in the mast cells is in the form of the heparin-complement complex. In view of the ability of heparin to form compounds with proteins, lipids, etc., and to peptize colloids such as barium sulfate, observed by Fisher, it is not surprising to find that even purified preparations of the substance are not homogeneous by various chemical methods (372, 373). Further studies have been reported of the reaction of heparin with proteins (374, 375). Space does not permit considering the many reports of sulfonated polysaccharides with anticoagulant activity. In comparing their activity with heparin, it should be emphasized that the unique anticoagulant properties of heparin are displayed on fresh whole blood rather than on any particular component of the clotting system. Pantlitschko *et al.* (376) report that on conducting Halse's test for thrombolytic or fibrinolytic activity *in vivo*, their sulfurated hyaluronic acid and also liquemin showed no activity, in contrast to the activity observed with heparin, although they comment that in no case did they observe with heparin the very marked fibrinolytic activity reported by Halse.

Several reports have been published regarding the metabolism of injected heparin. Marbet & Winterstein (377) have studied the urinary metachromatic product obtained after the injection of heparin, uroheparin, and have shown that it has the same combining power and sulfur content as the injected heparin, but lower anticoagulant activity and lower molecular weight. Jaques, Napke & Levy (378) find that excretion of metachromatic activity depends very greatly on the dosage level. At presumably physiological levels very little metachromatic activity appears in the urine, the heparin being disposed of by heparinase (379).

The only fully proven case for the liberation of heparin from the mast cells and its appearance as a circulating anticoagulant is in anaphylactic and peptone shock in the dog. Scroggie & Jaques (380) have succeeded in obtaining the release of heparin by the perfusion of antigen through the isolated liver of the sensitized dog and find that anoxia, etc. interferes with the release. Allen (see 5) has come to the conclusion that the appearance of heparin in the circulation in irradiated dogs is likewise an anaphylactic response rather than the result of irradiation. He attributes this to sensitization from the blood transfusions required for survival of these animals (in addition see 381). Bell (382) has described a case of idiopathic "hyperheparinemia." This individual showed a very prolonged coagulation time (approximately 2 hr.) which was normalized by the addition of protamine and therefore is true heparinemia. The patient was controlled with protamine and with desoxycorticosterone (DCA). The presence of heparin in certain effusions into body cavities has been satisfactorily demonstrated by the fact that these produced blood incoagulability which was completely reversed by protamine [by Fontaine (383) for extrapleural, intrapleural, and extra articular effusions of blood and by Palla (384, 385) for fluid from ovarian cysts.] Burstein (386) confirms the old observation of Doyon that the injection of atropine into the mesenteric vein of the dog causes the secretion of very large amounts of heparin and incoagulability of the blood. Reid (387) reports that tubocurarine is a heparin liberator as well as histamine liberator in the dog. Glick (388 to 391) has studied intensively the nonspecific hyaluronidase inhibitor in serum. Reference has already been made to the inhibitory activity of heparin on hyaluronidase. The inhibitor isolated from plasma is metachromatic, can be precipitated by protamine, and can be measured by the procedure for heparin of Jaques, Monkhouse & Stewart. The purified material shows no anticoagulant activity but this may be partly due to the fact that it contains considerable thrombin. The results suggest that the inhibitor studied by Glick is a heparin of low anticoagulant activity. The phenomenon of Hahn and Weld (391b, c) that heparin can reduce lipemia has been the subject of no less than 40 reports during the past two years. Although outside the scope of this review for detailed consideration, it should be pointed out that many of these investigators have used chiefly the protamine index or similar methods, and conclusions to the effect that heparin blood levels are significant factors for

the state of fat and cholesterol in the blood are premature. Levy & Swank (392) demonstrate that the liberation of heparin in the dog by anaphylactic shock, etc., may or may not be accompanied by clearing when the animal is lipemic, and vice versa, and this also suggests caution in ascribing a physiological role to heparin in this connection. The phenomenon is apparently related to the ability of heparin to combine with proteins together with lipids (394, 395) described by Fischer (393). Protamine and toluidine blue are active antagonists of heparin *in vivo*, and this has many applications in physiological experiments and clinically. This has been limited in the past by toxicity. An investigation of the toxicity of protamine by Jaques (298) illustrates that this occurs chiefly in the dog and can be avoided. Leitch & Haley (396) have studied the pharmacological properties of toluidine blue and related dyes. Esteve *et al.* (397, 398) have introduced  $\alpha$ -naphthylamine-4-sulfonic acid as a hemostatic agent in place of toluidine blue, as it has no heparin-like action.

Interest continues in other natural anticoagulants and particularly in plasma antithrombin. It is evident that this phenomenon can be due to a number of mechanisms: absorption of thrombin on fibrin, inhibition by heparin plus a co-factor, and a separate plasma component which neutralizes thrombin activity and which is usually referred to, as plasma antithrombin. In addition, Seegers (399) reports another antithrombin reaction which appears to be due to Ac-globulin. Other studies on antithrombin and other anticoagulants have been reported (400 to 409).

The mast cells have been a subject of controversy since their first description by Ehrlich. In part this is due to fact that the solubility properties of the granules appear to vary greatly with different species, and in many instances they dissolve very rapidly, so that different results are obtained with different techniques by different workers. Further evidence in favour of a close relationship between heparin and mast cells has been provided by Ehrlich *et al.* (410) who demonstrated a large number of mast cells in a case of elephantiasis scroti and successfully extracted heparin therefrom. This is actually the only report of heparin having been extracted from human tissue. Julén, Snellman & Sylvé (369, 370) report that both their histological methods and cytologic fractionation studies indicate that the metachromatic substance of the mast cell is not in the granules but in the cytoplasm. These conclusions have been refuted by Zollinger (411) and Freiberg, Graf & Aberg (412). With the exception of the dog, there has been little of evidence that heparin contributes anything to the clotting system as an anticoagulant, and, in the case of those species where heparin has relatively low anticoagulant activity, one wonders if this may not represent some other function. Asboe-Hansen (413) assumes that under the influence of hormonal action the mast cells secrete the mesenchymal mucopolysaccharide, hyaluronic acid, perhaps by way of a preliminary sulfuric acid-containing stage resembling heparin. However, the demonstration that the amino group in heparin has a sulphuric acid substituent and not an acetyl group differentiates the heparins chemi-

cally from hyaluronic acid and other polysaccharides, and the report of Balazs, Hogberg & Laurent (414) makes this suggestion very improbable. The precipitation of collagen by heparin (415) is a property of many substances (416). The periodic acid-fuchsin staining reaction of Hotchkiss is finding wide use in histology as a stain for polysaccharides (cf. 417). The mast cell granules react with this reagent to give a strong red colour in man and rhesus monkey, although, in contrast, the mast cells from pig give a moderate colour and those from rats give a poor one. As indicated above, Jorpes, Werner & Aberg (364) and Freiberg, Graf & Aberg (412) have shown that heparin monosulfuric acid, but not heparin, gives a positive reaction with this test, and it is believed that this is the substance in the mast cells reacting with this agent. The reaction suggests that the anticoagulant may be formed by the addition of sulfuric groups, but it is also possible that this substance represents degradation products of heparin. Drennen (418) reports that whereas all the granules of mast cells are stained metachromatically, only a proportion of the mast cells are stained by the periodic acid-Schiff reagent. As discussed under methods, metachromasia with toluidine blue is given by many high molecular weight acids, even though heparins appear to have particularly high activity. Of the substances apt to be confused with it are hyaluronic acid and nucleic acid (419). Even the use of hyaluronidase and ribonuclease may yield ambiguous results, since heparin is an effective inhibitor of both enzymes (420, 421). There are some reports that suggest a relation between the mast cells and extra-cellular metachromasia (422, 423, 424). Distribution and morphological studies on the mast cells have been reported (425 to 428). Hissard, Monocourier & Jacquet (429) report after intradermal injection of heparin a direct and progressive transformation of fibroblasts into mast cells. Paff & Bloom (430) have studied the release of metachromatic substance by mast cells of dogs in tissue culture which appears to be by degeneration and death of the cell. Drennen (418) concludes that in tissue edema is the effective stimulus to changes in the mast cell. One of the remarkable effects with tissue mast cells is the very extensive alterations in morphology and number which can take place (without any detectable heparin in the blood) after x-irradiation (431) and cortisone (413, 432), but Schoch & Glick (433) and Devitt *et al.* (434) can find no consistent effect when allowance is made for the normal variation in count and morphology.

*Vascular factors in hemostasis.*—Roskam (12) has published a monograph on hemostasis during the period under review. This is particularly useful for the review of factors producing the hemostatic plug, the mechanism of platelet agglutination, and hemostatic vaso-constriction, and also in that it presents Roskam's extensive investigations on the bleeding time and correlates his very extensive investigations on epinephrine, adrenochrome, and related compounds. Hugues (11) reports microscopic observations on blood vessels subjected to trauma, a technique developed by M. Zucker and others. Hugues states that he is unable to observe that hemostasis results

from a series of independent phenomena which follow each other and that the vasoconstriction and the collecting of the platelets at the wound occur equally early and appear to be related with the later appearance of fibrin filaments. He could not confirm any role played by clot retraction.

Roskam has demonstrated that adrenalin has an effective hemostatic action in doses which result in physiological concentrations in the blood ( $10^{-8}$ - $10^{-9}$ ) and that this action is due to an oxidation product, such as adrenochrome. Another smooth-muscle stimulating substance of significance in this regard which has been the subject of a number of recent investigations is 5-hydroxy tryptamine (serotonin or enteramine), which originates from the platelets during clotting. Page (435), Freyburger *et al.* (436), and Rand & Reid (437) identify the active portion of serotonin as 5-hydroxy-tryptamine, serotonin being actually 5-hydroxy-tryptamine creatine sulphuric acid. This completes the identification of the platelet factor, although the complete isolation of serotonin from platelets has not been carried out. The effectiveness of serotonin as a hemostatic agent has been demonstrated by Correll *et al.* (161). They demonstrated serotonin causes a prompt cessation of bleeding of the severed rat tail (1 min. compared to 8 min. for controls) whereas epinephrine, tyramine, and adrenochrome were inactive. Some indication of the mechanism whereby ACTH affects hemostasis is provided by Robson & Duthie (438), who have observed a pronounced rise in capillary resistance with x-irradiation, nitrogen mustard, epinephrine (Adrenaline), insulin hypoglycemia, etc., known to be stimulators of epinephrine, and, through this, of the pituitary, and they suggest that a hypophyseal-adrenocortical mechanism is involved. They observe as great a rise in patients given ACTH or cortisone. In idiopathic thrombocytopenic purpura, the improvement in bleeding time corresponded with the rise in capillary resistance and not with change in platelet count. Cases of hypopituitarism had a low capillary resistance. The conclusion that the effectiveness of ACTH and cortisone in thrombocytopenia is chiefly due to an effect on the abnormal vascular fragility is also supported by Falloon, Greene & Losner (439). Lee *et al.* (440, 441) indicate that the serious effects of hemorrhage in scorbutic animals may be due to a moderate hemostatic deficiency combined with inability of the animal to survive a degree of hemorrhage not lethal to normal animals due to failure to produce vasoexciter material. Fulton, Akers & Lutz (442) have studied factors involved in hemorrhage from small venules in the hamster cheek pouch, produced by a stimulating microelectrode. Anticoagulants did not prevent but actually enhanced the formation of platelet plugs at the site of hemorrhage. As judged by the strength of stimulus required to produce hemorrhage there is an increase in vascular fragility but not capillary fragility after the administration of the anticoagulants. A development that has considerable possibilities is the demonstration by Samuels & Webster (443) that the application of heparin to the venous endothelium preparation prior to the application of toluidine blue results in outlining the intercellular cement substance metachromatically. Unless heparin or indigo tetrasulfonate



are first applied, the basic dye does not attach to the cement substance, so that it is evident that heparin is combined with the cement substance. As they also show that platelet deposition and inception of thrombus formation occurs only at the cement substance, this indicates a direct mechanism for the action of heparin. Heparin not only prevents deposition of platelets on the intercellular cement in normal veins but it limits, although it does not prevent, local thrombosis from occurring on injured endothelium.

*Miscellaneous.*—Schneider & Zangari (444) report a shortening of blood clotting time and 12.5 per cent prothrombin time after 30 min. of vigorous muscular exercise. Similar changes were observed in emotional states. Campbell *et al.* (445) concludes that there is no significant change in clotting with thermal burns. Lepp, Chubaty & Jaques (446) report experimental frostbite causes an increase in the prothrombin time of rats and makes rabbits much more sensitive to the dicumarol anticoagulants. Decreased coagulability occurs in hibernation (447 to 450). A number of investigations have been reported of the clotting system in pregnancy, as, since Woodridge, there have been suggestions that intravascular clotting is a factor in eclampsia. Nakano (451) reports that the clotting time of adult healthy females fluctuates periodically as in the case of the basal body temperature, with minimum values at time of ovulation and maximum prior to menstruation, and decreases with pregnancy up to the seventh month. Olwin & Allen (452) report increased coagulability by the two-stage prothrombin time in pregnancy. Loeliger & Koller (334) and Cataldi, Mereto & Pastorino (453) find in the great majority that this is due to an increase in Factor VII, while in a minor number it is due to an increase in prothrombin. Schneider, Seegers, Page, and others have published a number of reports on coagulation changes in pregnancy, particularly in connection with placenta abruptio and eclampsia (cf. 28, 32).

Eisenmenger *et al.* (454) review the recent literature on ACTH and clotting and report a series of cases with hepatic cirrhosis treated with ACTH which showed clinical hypercoagulability. Cosgriff, Diefenbach & Vogt (455) report that ACTH, and cortisone especially, produce a hypercoagulable state of blood with shortening of the venous clotting time and the heparin-retarded clotting-time and with numerous thromboembolic episodes, while Fahey (456) finds no effect of ACTH on the clotting time determined by the Allen method. McGraw *et al.* (457) reports that ACTH has a two-fold effect on clotting and may produce hypercoagulability or hypocoagulability. Twelve patients with thrombosis were treated with corticotropin with considerable improvement and showed an elevation of the protamine index and an increase in the one-stage prothrombin test. Margulis (458) and Chevallier, Fiehrer & Tadzer (459) have reported studies with various clotting tests on patients receiving ACTH and cortisone and after surgery or normal delivery. The results with ACTH and cortisone were not uniform, but in general there was an increase in the protamine index and clotting time 4 to 8 hr. after the first injection of the hormone. This returned to normal in 24 hr. and then rose in a slight but steady manner to a peak on the third and



fourth day of therapy. After discontinuing the hormone, the protamine index was again elevated three to four days after withdrawal. There was no significant change in the one-stage prothrombin time, two-stage prothrombin time, Ac-globulin, or antifibrinolysin, but the diluted one-stage test showed a moderate increase during therapy. Eosinophils showed the usual fall. Similar results were seen in patients on surgery. Stefanini & Rosenthal (460) report two patients who developed hemorrhagic manifestations while on ACTH and conclude that this was due to ascorbic acid deficiency which developed as a result of the ACTH therapy. They attribute the hemorrhages to vascular injuries as found in scurvy and not to the relatively slight decrease in plasma prothrombin and Ac-globulin, the increased fibrinolytic activity, and delayed clotting in silicone. Van Creveld, Hoorweg & Paulssen (461) found that ACTH and cortisone reduced the anticoagulant found in a hemophilic. Other hormone effects on clotting have been observed (462 to 466).

In preparing this review, the writer has kept in mind the advice of that great seventeenth century English poet, John Donne, "Doubt wisely." He hopes that he has succeeded in following the advice, but in any case trusts the reader will apply it equally to this review.

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## PERIPHERAL CIRCULATION<sup>1,2</sup>

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### REGIONAL BLOOD FLOW

*Brain.*—Thanks largely to Kety's nitrous oxide method this has been another good year for the cerebral circulation in man.

The findings in hyperthyroidism are most interesting. Cerebral oxygen consumption in hyperthyroids is normal. Apparently thyroxine cannot stimulate the metabolic rate of brain. Cerebral blood flow was slightly increased probably because of intercurrent anaemia (1). The effects of the suprarenal hormones have also been assessed. Epinephrine scarcely affects cerebral vessels but norepinephrine constricts them strongly (2, 3). ACTH and cortisone cause parallel increases in arterial pressure and cerebral vascular resistance and do not affect central blood flow. The cerebral circulation shares equally in the increase in the general peripheral resistance (4).

There are a few papers on the effects of the blood gases. When oxygenation is normal the arterial blood CO<sub>2</sub> content appears to be more important in the regulation of the cerebral circulation than the pH (5). The effect of breathing oxygen at pressures of 3 to 5 atmospheres is to increase cerebral vascular resistance by about 50 per cent (6). On the other hand, in anaemia the circulation in the brain is increased; the hyperaemia subsides when 85 to 100 per cent oxygen is breathed, which upholds the view that it is due to reduced blood oxygen tension and viscosity (7).

"A man is as old as his arteries," is the saying; at any rate it is reassuring to see that mere age is without effect on cerebral blood flow (8). Nor is it much altered by amounts of alcohol sufficient to produce facial flushing and mild inebriation (9, 10); severe intoxication however increases it and depresses cerebral oxygen consumption (9). Coarctation of the aorta and priscoleline scarcely affect cerebral vascular resistance (11, 12).

Occlusion of the carotids in the cat abolishes the EEG<sup>3</sup> in 15 to 20 sec. Cats recover completely if the circulation is restored in 6 to 8 min., but if it is occluded for more than 10 min. they behave as if decerebrate (13). More information is available about the effect of cerebral ischaemia on the EEG (14).

*Liver.*—The sulfobromophthalein (Bromsulphalein) method continues to be popular for the estimation of hepatic blood flow. Some find that the dye escapes rather rapidly from the circulation (15, 16) and that it is reabsorbed

<sup>1</sup> The survey of the literature to which this review pertains was concluded in June, 1953.

<sup>2</sup> The following abbreviations are used in this chapter: EEG (electroencephalogram); VDM (vasodepressor material); VEM (vasoexciter material); ATP (adenosinetriphosphate); PAH (para-aminohippuric acid); RIHSA (radioactive iodinated human serum albumin).

from the gut (17), but others do not think these factors are of much significance (18, 19). Hepatic blood flows obtained from samples from different sites in the liver fall within the range of the normal resting flows (20). All of these results were obtained on animals.

A new method for estimating hepatic flow in man is based on the rate of disappearance of colloidal chromic phosphate from the circulation (21). Incidentally in dogs large particles of colloid gold disappear into the liver and spleen more quickly than small ones (22), and the rate of disappearance in the perfused liver is not directly related to the blood flow (23).

Estimated hepatic blood flow is normal in hypertensives. Shortly after splanchnicectomy it is increased compared with preoperative measurements on the same subjects, but within three months it is back to normal (24). In normal subjects insulin increases hepatic flow, probably because it releases epinephrine (25). In dogs narcotizing doses of alcohol do not alter liver blood flow (26), nor does ligation of the hepatic artery, though the flow is halved by ligation of the portal vein (27) and by Eck's fistula (28).

Hepatic blood flow in rats and rabbits has been investigated using a modification of the Gibbs heated thermocouple (internal calorimetry). Subcutaneous or intravenous epinephrine usually increases the flow in the conscious animal because the reflex vasodilator action excited by the rise in arterial pressure overcomes the local constrictor effect (29).

Other advances in the physiology of the hepatic circulation must be listed. Dogs with portorenal shunts survive ligation of all the hepatic veins; portal hypertension developed in 50 per cent, and so did ascites, but they were not related (30). Very little blood pools in the splanchnic bed when the portal pressure is raised suddenly; however, if the rise is maintained, pooling may be significant due to "delayed compliance" (31). Pressure pulses in the dog's hepatic vein exhibit a presystolic pressure wave followed by a negative "dip." They are propagated from the right atrium (32). The pressure obtained with a catheter occluding the hepatic vein in man does not differ significantly from that obtained directly from a portal vein radicle (33).

*Kidney.*—The effect of exercise on renal blood flow and function has been studied in man. Because of the use of renal and cardiac catheter the study had to be made with the subject lying down. During exercises with oxygen consumptions of about 1 l. per min. renal blood flow decreased about 20 per cent, but glomerular filtration did not alter (34). Nor do epinephrine and norepinephrine alter the glomerular filtration rate in man, although they constrict the renal vessels strongly (35). Modifications of Kety's  $N_2O$  method have been used to determine renal blood flow in anuria in man (36) and animals (37).

There have been important findings in animals. Alteration of the arterial blood pressure within wide limits does not affect renal blood flow ("autoregulation") (38, 39, 40). After haemorrhage, once renal vasoconstriction has occurred, autoregulation is impaired or abolished (38).

Many authors have studied the effect of oxygen lack. Renal constriction



in anoxia cannot be to preserve the blood supply to the brain because the survival time for normal and nephrectomized mice exposed to intense anoxia is the same (41). Circulatory changes in the kidney following occlusion of the renal artery have been observed directly under the dissecting microscope in the rat (42). In the dog reducing the arterial pressure to about 90 mm. Hg by partially clamping the pulmonary artery has the same effect on the circulation in the normal kidney as on that in the contralateral denervated one. A nervous mechanism is not involved (43). Although reduction of the oxygen content of the blood causes hyperaemia in the perfused kidney (44, 45), the filtration fraction decreases (45).

Renal blood flow 6 to 49 days after denervation is normal (46). Denervation increases the sensitivity of the renal vessels to the constrictor action of epinephrine and norepinephrine (47, 48). The hypersensitivity which develops is in the afferent arteriole. As in man so in the dog these hormones decrease renal blood flow in the innervated kidney without altering the glomerular filtration rate (48). The constrictor action of epinephrine is two to five times greater than that of norepinephrine (49).

Some unrelated findings must be listed. Increasing ureteric pressure in acute experiments almost abolishes renal blood flow and glomerular filtration (50). Great differences in the vascular bed of the rat's kidney are caused by thirst and water-loading (51). Blood flow in the urinary bladder has been examined by a calorimetric method. Raising intravesical pressure above a critical level decreases the rate of flow (52).

*Limbs.*—The plethysmograph is used for the study of the blood flow in human arms and legs. This has been another active year for plethysmographers. One of the topics has been the mechanism of the vasodilatation in muscle in exercise. Release of sympathetic constrictor tone in human muscle before exercise does not diminish post-exercise blood debt. The inference is that metabolites alone must be held responsible for the vasodilatation (53). Nor is post-exercise blood debt reduced when work is performed during the infusion of epinephrine. Contrary to Cannon's emergency theory the supply of "metabolically available" blood to muscle does not appear to be increased by this hormone. However the removal of metabolites does not depend critically upon the rate of flow (54).

The position of the limb affects the rate of the blood flow in the fingers and toes. It is most rapid when the limbs are raised about 15°. When they hang down distension of the veins excites a venoconstrictor reflex. The sympathetic is not involved (55).

The curious initial vasodilator action of epinephrine in the forearm and calf (muscle) has been confirmed. There is no concomitant increase in K or lactic acid in the femoral blood (56). Following the initial transient vasodilatation, epinephrine causes a smaller sustained dilatation lasting till the end of the infusion. Experiments on nerve-blocked and sympathectomized forearms lead to the conclusion that the sustained vasodilatation is not due to direct action of epinephrine nor is it a nervous reflex (57). Sympathetic de-

nervation alters the sensitivity of the muscle vessels to epinephrine. The initial transient vasodilatation is enhanced and the subsequent sustained one is impaired or abolished (58). The vasoconstrictor action of epinephrine on the vessels of the hand is sensitized fourfold by sympathetic denervation. Contrary to Cannon's law of denervation the amount of supersensitivity after ganglionectomy was no greater than that after preganglionic section (59).

The blood flow in the forearm and hand have been recorded after intra-arterial injections of histamine and acetylcholine. Acetylcholine was very rapidly destroyed in the blood stream. Following intrabrachial injections blood flow in the forearm was proportional to the logarithm of the dose (60). Moderate hyperventilation increases forearm blood flow, probably because of vasodilatation in the muscles. The vasodilatation was probably neurogenic (61).

The rate of  $\text{Na}^{24}$  clearance from the limb muscles has been studied by two authors (62, 63). It was exponential; the "half time" was 6 to 25 min. It was arrested by circulatory arrest; delayed by venous congestion, by locally applied epinephrine and by body warming; and increased by exercise and by locally applied histamine. Although affected by blood flow it was not directly proportional to it (62). In some experiments  $\text{Na}^{24}$  clearance was studied in the gastrocnemius of the leg while blood flow in the opposite calf was recorded plethysmographically. Epinephrine infusions had no effect on  $\text{Na}^{24}$  clearance, but they doubled the blood flow in the calf (63). The reason is not known.  $\text{Na}^{24}$  clearance from the subcutaneous tissue is increased by body warming (64).

The circulation in the fingers in patients with Pink disease has been studied by the finger temperature method during nerve blocks and body warming. The vessels are normal but sympathetic vasoconstrictor tone is excessive (65).

We know far too little about the vasomotor control of the veins. A short but most attractive paper has appeared on this subject. The effect of various procedures has been studied on intravenous pressure in a segment of a forearm vein closed distally by a valve and proximally by a clamp. Pressure rises of 5 to 50 mm. Hg were obtained during apprehension, after placing the opposite hand in ice water, and while breathing 5 per cent  $\text{CO}_2$ . The results of local and stellate nerve blocks suggest that this venous constriction may be mediated by the sympathetic (66).

There have been other findings on the venous circulation in the limbs that must be listed. The venous velocity in the legs as measured by  $\text{Na}^{24}$  clearance lying down is about double that while standing or sitting (67). Pressure in the superficial and deep leg veins has been studied in exercise and during coughing. During walking superficial venous pressure falls, but deep is not altered. Coughing or straining has the opposite effect (68). When the main artery of a limb has to be tied, is it better for the circulation to tie the main vein too? There is convincing evidence that the vein should not be tied (69).

It is interesting to read that one quarter of the blood in the heart, one quarter of that in the lungs, and one fortieth of that in the general circulation pools in the legs when we stand up (70).

Valuable results have been obtained on animals' limbs. The mechanism of the postcontraction hyperaemia in the cat's gastrocnemius has been analysed. The hyperaemia is reduced or abolished by cocaine, procaine, and botulinum toxin and is therefore probably neurogenic. It is unaffected by acute denervation and is probably an axon reflex. It may be mediated by cholinergic sympathetic fibres whose cell bodies are in the intermediate ganglia or in the muscle itself (71). During rhythmic activity muscle is at first acid, then alkaline, and finally acid. The first acid phase cannot be detected in the venous effluent. It is probably marked by the increased alkalinity of the blood caused by oxygen deficiency and hyperventilation. The alkaline phase is well seen in the venous blood; the second acid phase is delayed and reaches a maximum after the end of exercise (72). The relation between the duration of ischemia and that of the ensuing reactive hyperaemia has been compared in the femoral and carotid arteries. Hyperaemia lasted longer in the leg because the collateral circulation was not so good (73).

In the cat intravenous norepinephrine causes an initial transient increase in muscle flow followed by a decrease. The initial increase is passive, due to rise in the arterial pressure; the subsequent decrease is due to direct action on the muscle vessels (74). Other authors also find that intra-arterial noradrenaline constricts muscle vessels. So does epinephrine in "hypo-reactors"; in "hyper-reactors" epinephrine causes constriction followed by dilatation. Following adrenergic blocking agents epinephrine is a potent vasodilator. In "hyper-reactors," norepinephrine constriction is followed by vasodilatation. Adrenergic blocking agents do not block or reverse the constrictor action of either sympathomimetic in the skin (75, 76). The action of intravenous epinephrine on femoral blood flow is more complex. After section of the vagi and carotid sinus nerves, intravenous epinephrine causes marked increase in femoral flow. This vasodilatation occurs in the isolated innervated perfused leg and is reflex. The reflex is not elicited by the rise in the arterial pressure and is abolished by section of the thoracic dorsal roots (77). Another author has compared the action of epinephrine on the pressures in the small arteries and veins of the dog's hind limb. The results are tentatively interpreted as indicating a venule constrictor action of epinephrine proportionately greater than its arteriolar action (78).

The effect of oxygen lack has been studied on the blood flow in perfused rats hind limbs. It causes a redistribution of blood from the skin to the muscles. This effect is abolished by the adrenergic blocking agent dibenzylin (79). Immobilization of the dog's hind-limb in a cast for 14 days increases femoral arterial flow although the gastrocnemius loses one quarter of its weight (80).

*Foetal circulation.*—There has been a beautiful study of the circulation in the umbilical vessels and aorta of the foetal lamb. The diameter of the

umbilical arteries was not affected by the heart beat. These vessels receive two thirds of the blood flow through the descending aorta. Umbilical blood flow amounts to 300 to 400 ml./kg./min. Pressure in the umbilical veins is as high as 30 to 40 mm. Hg (81).

Foetal guinea pigs and rabbits are relatively insensitive to epinephrine and norepinephrine. Injections into the mother cause foetal bradycardia and hypotension as a result of placental vasoconstriction and foetal asphyxia (82). Similar responses were obtained by clamping the cord and by other procedures (82, 83). Atropine abolished the bradycardia, which was mediated by the vagus (83). Injections of pituitrin into the mother caused strong contraction of the uterus but no foetal asphyxia. This was probably because it did not constrict the uterine-vessels (82).

A new technique is described for perfusion of the sheep's placenta which can be used either for the measurement of equilibrium levels in the maternal and foetal bloods or for the rate of production of materials entering the foetal blood from the placenta (84).

The excised cow's udder has been successfully perfused. Decrease in blood  $\text{CO}_2$  content caused constriction of the vessels of this mammary gland (85).

#### NERVOUS CONTROL

*Afferent nerves.*—An important discovery is that human limbs are probably endowed with sympathetic afferent fibers to the vasomotor and other centres. This was inferred because radiant heat stimulation of the skin of the legs no longer caused reflex vasodilatation of the hand after lumbar sympathectomy (86). Afferents from human muscles may influence the circulation in exercise. This has been suggested because arresting the circulation in the legs at the end of a sprint on a stationary bicycle greatly prolongs the return of the arterial pressure to normal (87). For this investigation the auscultatory method was ingeniously modified so that determinations of the systolic pressure could be made every few seconds (88).

The vascular and respiratory responses to sciatic nerve stimulation have been analysed in detail in the cat. Low frequencies and fast conducting fibres of the A group are concerned with the fall of arterial pressure and initial inspiratory reaction. Higher frequencies and slower fibres of the  $\delta$  type are concerned with the rise in pressure and hyperpnoea (89). Distension of the gall bladder causes reflex splanchnic vasoconstriction and adrenal secretion. The path is by way of the right splanchnic through brain and spinal cord to the splanchnics of both sides (90).

*Baroreceptors.*—The pharmacological significance of the baroreceptors has been reviewed by Heymans (91). More cases of carotid sinus syndrome have been reported (92, 93). The seemingly heroic but fascinating procedure of carotid sinus nerve block in man has been repeated without mishap. Following this procedure, the rises in arterial pressure in normal and hypertensive subjects are about the same (+80/50 mm. Hg). The inference is that the impulse discharge from normal and hypertensive baroreceptors must be about

the same and that overstimulation of hypertensive baroreceptors must be prevented by lessened elasticity of the carotid sinus walls (94).

The importance of the sinus walls has been investigated from another standpoint, that of their smooth-muscle tone. Increasing the tone by locally applied noradrenaline stimulates the baroreceptors and depresses the arterial pressure. It also shields them so that their responses to intrasinus pressure changes are reduced (95, 96). Whether changes in carotid arterial tone affect the baroreceptors in the normal animal is not known; perhaps they do not, for stimulation of the sympathetic innervation does not do so (97).

There are further important discoveries. Pulsatile flow stimulates the baroreceptors more effectively than nonpulsatile. In pulsatile flow the impulse discharge occurs in bursts during systolic and early diastolic (98). After carotid occlusion in the dog and cat, intrasinus pressure at first falls below the threshold of the baroreceptors, but it soon recovers partially as blood flows back from the circle of Willis (99). Changes in blood temperature have but a transient effect. The increase in frequency discharge caused by a rise of 1 to 2°C. last less than one quarter min. (100). Veratrin sensitizes the baroreceptors and chemoreceptors to their natural stimuli (101). Incidentally carotid occlusion decreases lymph flow from the left thoracic duct, but flow from the right duct is not affected. Splanchnic vasoconstriction may be the explanation (102). It is most interesting to see that the well-known rise in arterial pressure following sinus and aortic denervation is unobtainable in adrenalectomized animals (103).

*Central nervous system.*—It is convenient to begin with the effects of stimulation of the motor area. In the dog stimulation of certain parts of it cause vasoconstriction in the curarised hind limb; these parts are called "vasoconstrictor centres" (104). In cat stimulation of it depresses the arterial pressure. After section of the pyramidal tract however this fall is unobtainable, and it appears that this tract must contain vasomotor fibres (105). Circulatory disturbances in convulsions have also been investigated. Four phases are recognisable in the variations in arterial pressure accompanying convulsions induced in rabbits (106). Epinephrine prolongs convulsions. Some think this is because of its hypertensive effect (107); others believe it is due to specific action (108).

Descending to the hypothalamus there is conclusive proof of the existence of a "vasodilator area" for skeletal muscle in the supraoptic region. The path is via sympathetic cholinergic vasodilator fibres. It is suggested that this centre is responsible for the primary vasodilatation in muscle during exercise (109, 110). Lower still in the medulla another author has mapped the pressor and depressor points with meticulous care. The pressor points are mostly dorsomedial and ventrolateral quadrants of the reticular formation of the anterior medulla, shifting centrally and dorsomedially as one proceeds caudally until the most posterior levels are approached, where these points shift to the most lateral points of the bulb. Depressor points have a much less constant distribution, most often being found in the

central parts of the reticular formation and shifting somewhat ventrally in the caudal regions of the bulb (111).

Circulatory problems to do with cerebrospinal fluid may now be mentioned. The rise in arterial pressure caused by intracisternal injection of potassium in the dog is a result of combined stimulation of the sympathetic and secretion of a vasoconstrictor substance from the pituitary (112). Curious swings of arterial pressure of up to 120 mm. Hg can be induced in bled dogs by elevating the cerebrospinal fluid pressure. A plausible hypothesis has been suggested (113).

*Efferent nerves.*—A question of great fundamental interest is the relation between the impulse frequencies in a vasomotor nerve and the intensity of the vasoconstriction. This has been examined in the heart-perfused rabbit's ear. The strongest constriction was excited by a frequency of 25 per sec. Frequencies below 0.5 and above 60 were ineffective. Small frequency or arterial pressure changes often caused a marked change in the resistance to flow (114). The nature of the sympathin released at the vasomotor endings in the rabbit's ear has also been examined. Colorimetric, biological, and chromatographic methods show that it contains epinephrine and even larger amounts of norepinephrine (115).

Some vascular problems connected with the sympathetic innervation and denervation of human limbs have been reviewed (116). In the dog there is another proof that vasomotor fibres to the limb muscles travel in the mixed nerves and not along the arteries (117). To assure complete preganglionic denervation of the distal part of the dog's hind leg extirpation of the entire lumbar trunk as far as L 6 or L 7 must be continued with section of spinal nerves (118). In this animal stimulation of the Th 12 to L 2 causes vasoconstriction, but stimulation of L 3 causes marked vasodilatation (119).

#### CENTRAL BLOOD PRESSURES

*Arterial.*—Many physiologists attribute the familiar increase in arterial blood pressure during emotional stress to vasoconstriction. However it seems to result from increased cardiac output; total peripheral resistance decreases (120). This is not surprising, for similar changes take place in man during infusions of epinephrine.

A fresh explanation is suggested for the Korotkoff sounds. The taps arise when the arterial wall moves outwards with enough force to "sound" the skin. The murmurs are due to turbulence (121). Intra-arterial recording of the arterial pressure in man has been used to study the effects of respiration (122, 123, 124) and also those of the Valsalva manoeuvre (125) and of the pulse volume (126). During large respiratory arterial pressure waves, changes occur both in the stroke volume and also in the peripheral resistance (122).

Useful results have been obtained in animals. The arterial pressure remains constant for 2 to 3 yr. in healthy dogs. Dietary experiments do not permanently alter the basic level (127). Pressure contours have been recorded simultaneously in many of the large arteries of the dog. Brachial pressure is



higher than aortic; mesenteric renal and femoral pressure are lower (128, 129). An explanation is offered for the dicrotism in the femoral pulse; resonant oscillation of the entire aortic blood column occurs due to the equivalent wavelengths of the thoracic and abdominal femoral segments, the lowered resistance of the origin of the splanchnic vessels, and the increasing resistance of the femoral vascular bed (130). A very pretty study has been made of the phasic velocity of flow in the rabbit's aorta by cinema photography of injected air or dye bubbles at 1500 frames per sec. (!). Peak mean velocity early in systole is 60 cm. per sec., falling to zero at the end of systole. In diastole there is first retrograde flow and then stasis. Backflow may be 25 cm. per sec. and amount to one third of the systolic forward flow, and is caused by seepage of blood into the visceral arteries; it does not occur in every part of the aorta (131). In early systole the flow is parabolic, but it becomes turbulent before the peak velocity is attained. The Reynolds number is about 300. Eddying occurs at the aortic bifurcation during forward flow (132). Another author has examined phasic velocity of flow in the dog's femoral and carotid arteries using the electromagnetic flowmeter. Normally there is no back flow, but it appears in both vessels when the peripheral resistance is increased somewhat by epinephrine (133).

A number of papers have appeared on the relations between pressure, flow, and resistance. There has been a really good investigation on peripheral denervated preparations of the formula  $F = cP^n$ . The value of  $n$  depends on "passive" and "active" factors. Distension of the vessel's walls and change of apparent viscosity are "passive" factors, both of which tend to increase the value of  $n$  above unity. "Active" reactions of the smooth muscles tend to decrease " $n$ ." Tone is believed to be basically myogenic, although strongly influenced by external factors (134). Another author has obtained valuable data of the influence of the erythrocyte concentration on the pressure-flow relations in the dog's hind leg. Since the logarithmic slopes of the pressure flow curves were equal for all haematocrit values the relative apparent viscosities were independent of variations in pressure. However, when the vessels are maximally dilated the relative apparent viscosities are intimately dependent upon pressure. The relative apparent viscosity *in vivo* was much less than that observed in a high velocity viscometer (135).

The relative effects of different procedures on venous return and peripheral resistance have been separated in open-chested dogs. Venous return is gauged by the height of the blood in a venous reservoir, peripheral resistance by the arterial pressure, the output being kept constant by a pump feeding the right atrium. Epinephrine and norepinephrine increase both venous return and total peripheral resistance (136). Such results are not all applicable to the unanaesthetized intact human subject, however, for physiological doses of epinephrine cause overall vasodilatation in man.

The concept of "critical closing pressure" has been given strong support by further experiments on the rabbit's hind limb. Residual arterial pressure was higher than venous pressure in every one of 30 experiments. The average



difference was about 10 mm. Hg. When the venous pressure was artificially raised to about 20 mm. Hg the residual arterial pressure exceeded the raised venous pressure also by about 10 mm. Hg. This elevation of the "critical closing pressure" may be due to a vasomotor reflex from the veins (137).

Pressure volume diagrams of post-mortem specimens of human and bovine aortas have been obtained and related to age, hysteresis, and other factors (138). The coefficient of elasticity of the dog's arterial system has been calculated from the arterial pressure changes, periodic volume changes imposed by a piston pump (139).

*Venous.*—In many subjects the determination of central venous pressure from the height of the column of blood in the jugular vein is difficult or impossible. Attention to a few practical details overcomes the difficulty in 80 per cent of subjects. The pressure is usually between  $-0.5$  and  $-1.5$  cm. Hg (140). In cases of congestive heart failure, valid measurement of central venous pressure can be made by placing the subject on his side and recording from the dependent antecubital vein. In these patients haemorrhage did not appear to cause constriction of the central veins (141). As regards the effect of positive and negative artificial ventilation on central venous pressure in man, the results show no difference. From the standpoint of the circulation one seems as good as the other (142).

An ingenious flowmeter embodying a combination of Pitot and resistance meter principles has been used to determine the respiratory variations in vena caval flow in dogs (143, 144). Further information is now available about the dynamics of venous collapse in the superior vena cava (145) and about relationship of abdominal pressure to venous pressures in the lower part of the body (146).

*Hypertension.*—This subject is so specialised and endocrinological that the present reviewer's comments would be of no value. References to papers on hypertension are included, as is traditional in this chapter on the peripheral circulation. For the reader's convenience, those concerning man (147 to 153), the dog (154 to 165), and the rat (166 to 177) have been grouped together.

#### TEMPERATURE

A very nice study is reported of the circulation in the arm of the Eskimo in the Canadian Eastern Arctic as compared with that in the arm of the Canadian medical student in a temperate climate. In the cold Arctic, Eskimo hand blood flow was twice that of the white man, and it responded more slowly to local cold; these differences are of teleological value (178). In the forearm, except in hot water, blood flow in the Eskimo was also greater. Increased heat production may be the explanation. In cold water, though the blood flow in the Eskimo's forearm is greater than that of the white man, the temperature of the muscle is less. This anomaly may be explained by a greater flow of cold venous blood from the hand (179). There have been further experiments on the effect of cold on the circulation in the fingers.

In denervated fingers cold vasodilatation gets more conspicuous as sensation returns. This upholds the idea that it is caused by a local axon reflex (180). Persons whose serum has a high titre of cold agglutinins are usually prone to numbness and cyanosis of the fingers on exposure to cold. Experiments show conclusively that the digital vessels become blocked with cold agglutinated red blood corpuscles (181). It is interesting to note that aggregation of the red corpuscles following a fatty meal may sometimes completely stop the circulation in the cheek pouch of the golden hamster (182). Yet another mechanism, namely blood viscosity, appears to be responsible for the decrease in blood flow in the perfused rabbit ear in response to cold (183).

Rapid hypothermia has been induced in dogs by drawing blood from the veins, cooling it, and pumping it back into the arteries. Animals cooled thus to 29°C. survived, but those cooled below 27° died. After cooling, arterial pressure and cardiac output were about halved (184).

Work on isolated arteries must now be mentioned. Isolated swine arteries manifest a seasonal variation in reactivity. In winter the reaction to epinephrine is shorter and that to histamine is longer than in summer. It is suggested this may be explained by seasonal variations in the level of thyroxine (185, 186, 187). Curious effects of temperature have been recorded on isolated ox carotids. When the temperature is raised progressively from 10°C. to body temperature three phases are recognisable in the response of the vessel: contraction at about 15°, followed by dilatation, and finally, again, contraction. The temperatures at which reversals of the response take place are influenced by the load on the vessel wall (188).

#### HAEMORRHAGE

Edholm has reviewed the effects of haemorrhage in man. Unless fainting occurs, as happens in 50 per cent of subjects, bleedings of 1 litre do not affect the arterial pressure and heart rate; cardiac output is reduced by 20 per cent. There is vasoconstriction in the splanchnic area, kidneys, and possibly in the skin, but not in skeletal muscles. Contraction of the veins may be of more use than the blood reservoirs. Hemodilution is slow; it takes 24 hr. to restore the blood volume (189). The optimum capacity for human work has been determined before and after  $\frac{1}{2}$  l. bleedings. Immediately after bleeding it is reduced by 8 per cent; 2 to 6 days after bleeding it is unaltered, and 8 to 10 days after bleeding it is actually greater by 7 per cent (190).

Numerous experiments have been done on animals. The pressure volume relations for central venous and pulmonary arterial pressure during haemorrhage are almost parallel. Pulmonary resistance probably increases (191). Bleedings of 1 per cent of the body weight in dogs cause proportionate decreases in cardiac output, splanchnic blood flow, and splanchnic oxygen consumption (192). After bleedings to 45 mm. Hg in rats, portal pressure is halved and direct microscopy discloses reduction in blood flow and narrowing of the sinusoids, central venules, and sublobular venules (193). As there is no relation between irreversible shock and portal venous pressure, pooling

of blood in the splanchnic area is not likely to be the cause of irreversible shock (194). Normal dogs are less able to withstand prolonged reduction of the arterial pressure to 40 mm. Hg than are dogs with hepatic arterialization (right nephrectomy; right renal artery to central end portal vein; distal end portal vein to right renal vein). Perhaps this is because arterialization reduced the rate of ferritin formation (195). In the kidney marked degenerative changes occur when the arterial pressure has been reduced to 70 mm. Hg for 24 hr.; clearance is impaired, and nonprotein nitrogen exceeds 100 mg. %. However haemorrhage will not produce death from renal failure unless nearly all functional renal tissue is destroyed (196). Early in progressive haemorrhage the internal mammary arteries are relatively less constricted than the coronaries, probably because of hyperventilation. Later when the animal becomes cyanosed the situation is reversed (197).

The effect of transfusions has received much attention. It is good to see that intravenous infusions restore the arterial pressure just as effectively as intra-arterial ones (198, 199, 200). Valuable information is available on the results of injecting solutions of dextran (201, 202, 203) and of polyvinylpyrrolidone (204). The best results with saline were obtained by the immediate injection of an amount equal to about 10 per cent of the body weight (205). Saline infusions of three times the plasma volume treble the rate of passage of albumin into the tissues and more than treble the rate of its return by the thoracic duct, so that the total amount in the blood is increased. The extra is mobilized from the tissue spaces (206). In the dog saline infusions of 3 l. scarcely affect the arterial and venous pressures or the heart rate (207).

It is confirmed that *N,N*-dibenzyl- $\beta$ -chloroethylamine (Dibenamine) increases the chances of survival after severe haemorrhage (208); the mechanism has been investigated (209).

#### FAILURE AND SHOCK

Sharpey-Schafer has summarised recent work in his laboratory on the peripheral vascular changes associated with heart failure, fainting, and local ischemia (210). Peripheral vasomotor responses to acute coronary occlusion have been studied in the dog. Vasoconstriction frequently occurs in the hind limb; never vasodilatation. There is no evidence for the existence of a reflex vasodilator mechanism from the ischemic myocardium (211).

Other experiments on dogs show that the collapse of the arterial pressure induced by breathing nitrogen is mainly of cardiac origin. Peripheral failure is not responsible (212). In acute asphyxia induced by clamping the trachea suprarenal medullary secretion is increased thirty-fold; the proportions of epinephrine and norepinephrine remain the same (213). It is worth noting that even moderate anoxia, namely breathing 10 per cent oxygen, caused haemoconcentration and the loss of 25 per cent of the plasma volume into the tissues (214).

Ferritin (vasodepressor material) does not seem to be responsible for the

irreversible state in traumatic shock. Procedures which increase tissue ferritin do not affect the mortality of rats subjected to trauma in the Noble-Collip drum (215). Controlled blows on the occipital area of conscious dogs, in other words concussion, causes among other things increase in arterial pressure and in carotid blood flow. Similar changes occur in electroshock. Unconsciousness is not due to decreased cerebral blood flow (216). There are good studies of circulatory failure induced by electrolyte depletion (217) and of the post mortem changes caused by explosive decompression to 30 mm. Hg (218). A smooth muscle stimulating substance U has been found in the urine of dogs; it is increased by obstruction of the circulation in the legs (219).

The value of norepinephrine in the treatment of shock is becoming more and more apparent. Its clinical physiology has been reviewed by von Euler (220), and there are many reports of its use for sustaining the arterial pressure in patients for hours or even for days (221 to 225). Experiments on burnt mice show that, within an hour of transfusion with saline, plasma, or blood, nearly all the fluid can be recovered from the injured area (226). A variety of autonomic blocking agents has been formed to increase the survival time of dogs and rats subjected to stress of various kinds (227).

#### GENERAL AND REGIONAL ANESTHESIA

This short section is included because the circulatory changes during general and regional anaesthesia are of importance to both human and animal investigators.

One of the most significant findings is that anaesthesia alters the response of the circulation to haemorrhage. Bleedings of 1 l. induce vasovagal fainting and vasodilatation in the forearm in more than 50 per cent of normal subjects. This vasodilatation cannot be induced in lightly anaesthetised subjects, even by bleedings of 1.5 l. Apparently light anaesthesia abolishes the vasovagal reaction (228).

Other findings in man must be listed. The circulatory effects of  $2\frac{1}{2}$  hr. light cyclopropane anaesthesia have been fully described (229). Renal blood flow is substantially reduced by ether and cyclopropane but it is not affected by  $C_4$  (230).

Valuable information is forthcoming about the circulatory responses to spinal anaesthesia in man. Although anaesthesia extended to above Th 4 it is remarkable that there was no change in the splanchnic vascular resistance (231, 232, 233). It looks as if the decrease in right atrial pressure and cardiac output might be a result of release of venoconstrictor tone. Another author reports that the liver looked cyanosed and felt turgid and rubbery when the blood pressure fell to 45 mm. Hg during spinal anaesthesia (234). It seems that the controlled continuous intravenous administration of a thiophanium derivative (Afronad) is a good way for producing flexible and rapidly reversible hypotension in man (235).

There have also been findings in animals. Neither pentobarbital and cyclopropane nor ether caused much change in estimated hepatic flow in

the dog (236). In the dog's kidney however both cyclopropane and ether cause constriction of nervous origin (237). Pentobarbital sodium anesthesia in the dog depresses the arterial pressure and increases the heart rate and femoral arterial blood flow (238). Anesthetics have a harmful effect on the circulation in the dog's omentum (239).

#### PHARMACOLOGY

*Adrenergic blockade.*—A great deal of attention has been paid to the action of these agents. It is important to realize that their action may be altered by anesthetics. Doses which have a strong blocking action in the anesthetised animal may have none in the normal animal. For example DHO and SY 28 block the constrictor action of intracarotid injections of epinephrine on the vessels of the anesthetised dog's ear, but they have little or no such blocking action in the normal animal (240).

The hypotensive action of the hydrogenated alkaloids of ergot is no longer attributed to adrenergic blockade. Recent work shows that it is due to their action on the vasomotor centre. Moreover, when the centre or efferent fibres are out of action, their latent local constrictor effect may cause hypertension (241). Another author finds that in the kidney the local vasoconstrictor effect usually overcomes the vasodilator effect, especially in the denervated kidney (242).

It is interesting to have the fact pointed out that doses of *N*- $\alpha$ -methyl- $\beta$ -phenyloxyethyl-*M*-benzyl- $\beta$ -chloroethylamine (Dibenzyline) which reverse the arterial pressure response to epinephrine only block about half of its vasoconstrictor response. The same author finds that the constrictor response of norepinephrine is blocked at least as readily as that epinephrine (243). There are other studies of the blocking action of rigotine (244 to 247), 2-benzyl-2-imidazoline (Priscoline) (246, 247), Ilidar 6-allyl-6,7-dihydro-Sh-dibenz(c,e)azipine phosphate (246, 248), 3-pyridinemethanol (Roniacol) (247), and SY 2 and SY 21 (249).

*Ganglionic blockade.*—Hexamethonium, the ganglionic blocking agent, is being more widely used. Paton, who jointly with Ziamis discovered it, has reviewed its pharmacology (250). Calculations of the concentration time curves of hexamethonium in human plasma indicate that the drug is evenly distributed in the extracellular fluid. The thresholds for the reduction of arterial pressure, for elevation of the pulse rate and for interference with three separate pupillary functions varied from subject to subject and independently of each other. For a given subject the degree of reduction of the arterial pressure was directly proportional to the plasma concentration (251). The effect of hexamethonium on renal circulation and function has been studied in man and the dog. In man hexamethonium either did not affect the renal blood flow or decreased it (252). The same effect was found in the dog. Renal vascular resistance in the dog was reduced but this did not always compensate for the decrease in arterial pressure so renal blood flow was often decreased (253). The hypotensive action of subcutaneous injections of hexame-

thionium can be greatly prolonged by dissolving it in suitable solutions (254). Tolerance to hexamethonium can be induced by previous administration of its homologues (255). There are several reports of the use of hexamethonium in hypertension (256 to 260).

*VDM<sup>2</sup> and VEM<sup>2</sup>.*—Shorr & Baez have tried to explain why the reactivity of the mesoappendix to epinephrine is potentiated by renin. Ligation of the renal vessels abolishes renin potentiation. It is suggested that the potentiating substance which renin releases from the kidney is VEM (261).

Wiedeman & Nicoll have studied the reproducibility of the responses of the rat's mesoappendix to epinephrine. Less than 50% of the test animals showed a stable threshold. In a given animal the level of anesthesia had a marked effect upon the apparent threshold. The shifts of the apparent threshold due to changes in the level of anesthesia were as great as those claimed to be specific responses to tested agents. It is therefore concluded that the test cannot be used to prove the presence of vasoreactor substances (262).

*Serotonin.*—Several have investigated the pharmacology of serotonin, the constrictor agent present in defibrinated blood and plasma. In the cat it has a triphasic action on the arterial pressure which has been analysed (263). In the dog it has primary and secondary pressor actions which persists after sinus and aortic denervation (264). The pressor action of serotonin is unobtainable in dogs fed on a serotonin analogue (265).

*Hormones.*—Beta-hypophamine (Pitressin), infused intravenously, has very different actions on the arterial pressure in different animals. In the rat the rise in pressure is sustained throughout the infusion, but in the cat it subsides to some extent before the end of infusion, and by this time in the rabbit it has returned to the preinfusion level (266).

Tolerance to lethal doses of epinephrine has been further examined in the dog. It lasts about six months and is not specific. The arterial pressure response to a standard dose is not altered by tolerance. Death is due to intense constriction of the hepatic veins in the dog and to spasm of the pulmonary arteries in the cat and rabbit (267). Observations on spleen strips show that the constrictor action of epinephrine is far more powerful in the dog, cat, rabbit, and guinea pig than is the constrictor action of norepinephrine. In the dog epinephrine acts mainly on the capsule and trabeculae, and norepinephrine mainly on the vessels (268). Concentration activity curves for epinephrine have been obtained on spirally cut strips of rabbit's aorta, and their significance is discussed in the light of Clarke's equation (269). The mechanism of action of desoxyephedrine has been investigated on the dog's hind leg (270). A new pressor amine mephentermine (Wyamine) with norepinephrine-like activity has been described. In man it is a reliable pressor agent with little action on the heart (271).

Other advances must be listed. Both the anastomoses and the capillary channels of the rabbit's ear respond to small doses of histamine by dilatation and to large doses by constriction (272). The same applies to the vessel of the submaxillary gland with respect to acetylcholine and to epinephrine (273).

In the cat the depressor action of intravenous morphine is due to its central action and to liberation of histamine; in the rat it is mediated by the vagi (274). Cholinesterase inhibitors depress acetylcholine destruction and antidromic vasodilatation. The explanation is unknown (275). So also is the reason that the pseudocholinesterase inhibitor No. 1250 has actions resembling those of acetylcholine accumulation (276). The actions of nicotine and acetylcholine have been carefully worked out on the rabbit's ear (277). The pharmacology of a long acting depressor drug No. 48-80 has been described (278). The adenosinetriphosphatase content of the walls of arteries is far greater than that of the wall of veins (279).

#### ANATOMY

Investigators who put needles into the brachial artery will be interested to see that it has an anomalous course in 18 per cent of arms (280). The diameter of the human aorta has been related to various factors (281).

Authoritative histological accounts are available of the blood vessels in the choroid plexus of human and rabbit's lateral ventricles (282); also of those in the human pituitary (283), in the rat's adrenal (284), in the dog's tongue (285), and in the intestinal villi (286). Microscopic studies of the vascular bed in the frog's web and urinary bladder and in the human conjunctiva show no evidence of a structural unit built round a preferential capillary like "thoroughfare channel" like that described by Chambers and Zweifach (see 287). The elastic tissue of the human aorta has been studied with the electron microscope (288). The blood supply of the carotid body has been very well described in cats, dogs and rabbits (289) and so has the carotid rete in these animals and also in the sheep, goat, ox, pig, and rat (290).

There is more work on arteriovenous anastomoses. They exist in human stomach (291) and villi (286). In the dog's hind leg they are mainly in the pad (292). The "surface tension effect" which opposes the perfusion of air, mercury, and other fluids into small blood vessels has been used as the basis of a method for determining the largest vessel connecting the arterial and venous vessels of an organ. The maximum internal diameter of connecting vessels in the kidneys, intestines, and lungs was  $25\mu$  (293).

Though arterial grafts in dogs remain patent the plain muscle in the media disappears in a fortnight. It is converted into a tube with an intima and a hyalinized calcified media (294).

#### TISSUE EXCHANGE; LYMPH

Lack of space makes it impossible to do justice to this most important subject. The debt we owe to Professor G. Hevesy for pioneering the use of isotopes in biological studies is referred to in a lecture on the "History of Circulatory Research" (295).  $D_2O$  has been used in impressive studies. One author (296) finds that its disappearance reflects the exchange of water for the first minute only after injection. The rate determining factor for water distribution is at the cell level. Visceral cells exchange much more quickly



than muscle and bone cells (296). In the forearm 95 per cent of the  $D_2O$  left the circulation in the first minute probably by simple diffusion (297). In isolated heart and muscle the delivery rate was determined by the rate of the blood flow (298). Studies with thiocyanate, mannitol, and inulin fail to show any direct relationship between molecular weight and speed of capillary permeability (299). The kinetics of exchange of K have been studied by injection of  $K^{42}Cl$  into the ear vein of the rabbit. It seems impossible that the transfer could be by filtration alone (300). An improved method is described for measuring simultaneous tissue clearance of substance from the hind limb of the rabbit. The following substances are arranged in ascending order of rate of capillary transfer: inulin,  $SCN^-$ ,  $^{131}I^-$ ,  $PAH^2$  (301).

The rate at which T1824 and radioactive iodinated human serum albumin leave the circulation have been carefully compared in connection with their suitability for plasma volume determinations (302, 303, 304), and that of RIHSA<sup>2</sup> has been examined in hypovolemia induced by intraperitoneal injection of a nonelectrolyte solution (305). The counting dishes for RIHSA determinations must have perfectly flat bottoms (306). For labelling red corpuscles "Thorium B" is said to be better than radiophosphorus (307).

Measures for promoting lymph flow have been studied in animals. Exercise, passive movements, massage and shivering are all of them very effective (308, 309). Even after death exercise increases lymph flow. On the other hand heating agents, diathermy and hyperthermia were ineffective (309). Lymphangiography has been used in man. Even with a tourniquet on the thigh dyes injected into the sole of the foot soon appeared in the lymphatics in the popliteal space (310).

#### METHODS

It is convenient to deal first with methods applicable to man. There is a thermistor radiometer for skin temperatures (311). For the calorimetric method for estimating finger blood flow to be reliable, one author finds that room temperature must be adjusted so that skin temperature is at least above  $25^{\circ}C.$ , and preferably above  $29^{\circ}$  (312). In plethysmography transducers have been employed in continuous recording apparatus (313, 314). If a procedure  $P$  has a circulatory effect  $C$  and a respiratory effect  $R$ , is  $C$  due to  $P$  or  $R$ ? The answer can be obtained by an ingenious method which enables the effect of  $R$  upon  $C$  to be assessed in the absence of  $P$  (315).

There is a simple method for obtaining a continuous record of the mean arterial pressure in man. An intra-arterial needle communicates with a chamber containing a thin rubber fingerstall which transmits the pressure via a water-filled tube to a conventional manometer. All except the manometer is sterilized before use (316). The performances of the Lilly capacitance manometer and the Strathan strain-gauge have been compared in a small series of experiments. For most purposes the strain-gauge was preferred because of its greater stability (317). The conversion of Millikan and Wood type oximeters into direct recording instruments has been described

(318), as also have mechanically driven syringes for continuous infusions (319, 320).

The use of perfusion pump devices for animal work has been critically studied. The results indicate that in almost any method involving even slight handling of the arterial blood vasodilator agents will be released from the blood cells. The most important is probably ATP<sup>2</sup> from the erythrocytes. Venous outflow recorders are by far the most indulgent of the direct methods (321). New flowmeters include an electrically recording bristle type for volume and phasic changes (322), an easily cleaned Gaddum outflow recorder (323), a closed circuit low resistance drop-chamber which avoids evaporation (324), and others (325, 326). There is a device for obtaining the electric flowmeter zero without stopping the flow (327). The Gibbs heated thermocouple has been adapted for determining the thermal conductivity of blood flow in solid organs (328).

We are indebted to Wetteler for introducing the manometric sound and, independently, the electromagnetic flowmeter. He and a colleague describe a new sound, 3.2 mm. in diameter, working on the principle of the differential transformer. Its sensitivity is 30 mm. per 1 mm. Hg (329). A two-manometer photoelectric system has been designed for animal experiments (330). New techniques are reported for inserting needles into the great vessels of the thorax in unanesthetised animals (331) and for guiding catheters into abdominal vessels in anesthetised ones (332). A graphic method has been devised for arterial pressure recording in the unanesthetised rat. Greater objectivity is the advantage claimed over the microphonic method (333).

The arterial and venous pressures of primates in Aerobic rockets in flight have even been recorded continuously in the laboratory on terra firma (334).

#### BOOKS AND CONFERENCE REPORTS

"Adventures in Physiology, with Excursions into Autopharmacology" is not only the book of the year, it is one of the century. The book contains 30 papers and lectures mainly on histamine and humoral transmission. To these Dale has added his comments. It is the record of the way of a very great investigator (335).

C. J. Wiggers' "Circulatory Dynamics" is a welcome addition to the Modern Medical Monographs (336). In connection with monographs, the Physiological Society of Great Britain is sponsoring a new series. The first one on "Sympathetic Control of Human Blood Vessels" is mainly about the authors' plethysmographic studies of the circulation in human limbs (337). An annotated bibliography of about 2000 papers which appeared on the cerebral circulation in the decade 1938 to 1948 has been published by Physiological Reviews (338). The proceedings of three important conferences are available. The Ciba Foundation Symposium on the Visceral Circulation (339), the Josiah Macy Foundation Conference on Shock and Circulatory Homeostasis (340), and American Physiological Society's Panel Discussion

on the Interpretation and Significance of Alterations in Central Pulse Form (341).

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# HEART<sup>1</sup>

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## ELECTROPHYSIOLOGY

Electrocardiography still deserves first place as a means of studying the heart conduction system and disturbances of its rhythm. In an article on the history of electrocardiography Kossman (1) points out that the work of Frank N. Wilson summarizes the relation between electrocardiography and the laws of physics and that now new interests may arise in the comparison of electrocardiography and of vectocardiography with chemical phenomena occurring in the heart muscle.

Several papers (2 to 5) tend to the substitution of vectocardiography for electrocardiography. The problem which now arises is to determine whether the usual derivation and the precordial unipolar leads are reflections of local potentials or of the potential of the whole heart. Morin and co-authors (2) have demonstrated that the limiting distance within which the electrical field should be considered as homogeneous is nearer to the heart than is usually considered. Grishman *et al.* (4) also maintained that there is no local effect but that what is involved is the recording of the same vectorial phenomenon at various angles. Thaon (6) in an interesting study has tried to determine precisely the difference between a strictly local potential and the regional or topographical potential by using a "circular electrode." This circular electrode, which is made up of two concentric electrodes, gives information concerning the distribution of the electrical field at the point where the electrode is applied. Whatever the value of vectocardiography may be, supporters of the study of the standard unipolar electrocardiogram continue to record derivations, especially of posterior leads, for the diagnosis of posterior myocardial infarctions (7).

An interesting contribution to experimental electrocardiography has been made by Fabre & Linquette (8) which showed that in the dog opening of the thorax produces important modifications of the electrocardiogram. Lombard (9) devotes himself to the electrocardiographic study of small animals particularly of the rat. Investigations on the cellular electrophysiology of cardiac muscle seems to have been in the background during the period of this review (10, 11, 12).

## CONDUCTION SYSTEM

Read, Hegre & Russi (13) report a study on the atrioventricular conduction system in man employing both macroscopic and microscopic methods; the results favor the myogenic concept of conduction. Burchell *et al.* (14)

<sup>1</sup> The survey of literature pertaining to this review was completed June 1, 1953.

in a study of the spread of excitation through the ventricular myocardium showed that the path is complex but on the whole goes from the apex of the heart to the base.

The problem of the atrioventricular junction still raises some difficulties. Burchell (15) studied ventricular pre-excitation in the isolated perfused heart. For him the W. P. W.<sup>3</sup> syndrome is due to the existence of an abnormal pathway on the right face of the septum which was demonstrated in an isolated heart with exposed ventricular faces. On the other hand, Prinzmetal (16) does not accept the classical path involved in the W.P.W. syndrome. With high speed cinematography, he shows that one part of a ventricle contracts before the rest of the muscle and believes that the W.P.W. aberrant conduction may result from a failure of a part of the atrioventricular node to delay conduction through it to the ventricle (accelerated conduction). Some arguments against the classical explanation of the W.P.W. syndrome are based on drug effects obtained in some patients with this syndrome [Brinder, *et al.* (17)]. For example, atropine shifts the QRS toward normal; on the contrary digitalis favors the appearance of a W.P.W. pattern in a normal tracing. Lown *et al.* (18) studied a syndrome involving a short P-R interval with a normal QRS complex and a paroxysmally rapid heart action. Such tracings are different from the W.P.W. syndrome; the influence of age, sex, and duration of the QRS was considered. They did not study the wave at the beginning of the QRS complex which is supposed to result from pre-excitation.

On the other hand, de Boer (19), in an extensive study of the origin and nature of the Morgagni-Adams-Stokes syndrome, shows that the attacks can result from complete heart block which may arise during paroxysmal bradycardia or paroxysmal bigeminism; this possibility may be definitely neurogenic and in his case there was some change in the electrocardiogram. In a study of disorders of atrioventricular conduction, Latscha (20) reports a case in which changes of rhythm were observed during a surgical procedure for levocardia.

#### BUNDLE BRANCH BLOCK

Smith *et al.* (21), with high speed cinematographic control, studied the onset of contraction in the two ventricles during experimental bundle branch block; it was found that the onset of ventricular contraction on the side of the lesion was considerably delayed, being most marked in those animals considered to have complete block and less marked in those having incomplete block. Rodriguez & Sodi-Pallares (22) also studied the mechanism of complete and incomplete bundle branch block in dogs. The activation of the inter-ventricular septum passes from left to right and from below upward; the velocity of propagation is very rapid. Varying degrees of right bundle branch block do not modify activation of the left ventricle. Minor degrees of left bundle branch block delay the time of arrival of activation. The sense of activation is inverted. In right and left bundle branch blocks, a delay occurs

<sup>3</sup> Wolff-Parkinson-White.



in a small portion of the septum very near the right septal surface; thus the right and left ventricles are functionally independent, with no possible communication between the branches. Alzamora Castro (23) studied parietal focal block experimentally; injection of cocaine into a coronary artery produces a focal parietal block which disappears within 15 to 30 min. The tracings obtained at the beginning of right or left focal parietal block are similar to those considered as representative of right or left ventricular hypertrophy. Segers (24) studied the QRS complex in right or left complete or incomplete bundle branch block; it appears to him that right complete block effects the terminal phase of the QRS complex and only very rarely the initial phase. In a pathological and anatomical investigation, Sanabria (25) shows that in four cases of bundle branch block there was no alteration of the His branches; on the other hand in four cases with complete destruction of the His branches there was a perfectly normal record. Talmont and others (26a) made an extensive statistical study of bundle branch block. They found that in 6000 normal people right bundle branch block is rather more frequent than left bundle branch block; as is usually believed, right bundle branch block is found in right cardiac diseases and left bundle branch block in left ventricular diseases. They point out that incomplete left bundle branch block is rather frequently found (24 per cent) in syphilitic aortic insufficiency.

#### ATRIAL FLUTTER AND ATRIAL FIBRILLATION

The physiological disturbances in atrial flutter and atrial fibrillation have been studied by Wetherbee *et al.* (26b) by determining the ventricular rate response following exercise during fibrillation and after conversion to normal rhythm. They showed that atrial fibrillation diminishes cardiac efficiency as judged by the pulse rate changes after exercise. Broustet *et al.* (27) studied the oxygen saturation during atrial fibrillation: if the heart is normal, or if there is mitral stenosis, there is a diminution in the peripheral saturation after hyperventilation. After restoration of normal rhythm, the results are variable. Experimentally Brown & Acheson (28), employing the administration of aconitine as a means often employed to determine the existence of flutter and fibrillation, reached the conclusion that the flutter due to aconitine is different from the flutter produced by electrical stimulation. Von Ahn (29) describes a case of paroxysmal atrial fibrillation in acute nicotine poisoning.

In a symposium (30), Hecht, Katz, Pick, Prinzmetal, and Rosenblueth have discussed the nature of atrial fibrillation and flutter. First the discussion sought to determine whether the mechanism of flutter and fibrillation are identical. All agree this is the case. What is the mechanism in experimental animals? For Prinzmetal it is an ectopic focus, for Rosenblueth a circus movement. In discussing the mechanism of flutter and fibrillation in man, they were unable to agree either on the classical mechanism of circus movement or on the new mechanism involving an ectopic focus. No definitive conclusion is stressed. Scherf (31), in cases of experimental flutter or fibrillation caused by aconitine, has investigated the same problem and, for him,

all the known forms of cardiac flutter and fibrillation can be explained by the ectopic focus theory.

Comess (32) studied atrial flutter with complete heart block caused by a saddle embolus in a case of rheumatic valvular disease. Miller and others (33) studied the effects of procaine amide (pronestyl) in clinical atrial fibrillation. In twenty cases, doses from 500 mg. to 11.5 gm. per 24 hr. caused in every instance a disappearance of the abnormal rhythm. Brown (34) investigated factors related to the effects of quinidine in experimental atrial flutter. Cohn *et al.* (35) studied the paradoxical response to carotid sinus pressure. In chaotic heart disease, they showed that pressure on the carotid sinus causes flutter and fibrillation to disappear, with return to a normal sinus rhythm.

#### VENTRICULAR ARRHYTHMIAS

Malinov *et al.* (36) investigated the prevention of ventricular arrhythmias in the rat by inhibition of the thyroid and showed that hypothyroid animals are most resistant to development of ventricular tachycardia induced by intravascular injection of calcium chloride. Harris (37) described possibility of suppression of ectopic ventricular tachycardia accompanying acute myocardial infarction by the administration of magnesium sulphate and chloride; their results are dubious. Weisberg *et al.* (38) published a case of ventricular tachycardia persisting 23 days with no response to any treatment; at autopsy there were important lesions of the heart. January and others (39) report with very good results the treatment of eleven patients with paroxysmal ventricular tachycardia by means of the intravenous injection of quinidine. This suggests the possibility of treatment with procaine amide. A patient refractory to the usual treatment was effectively handled with pronestyl (40). Bistein & Harris (41) report the effectiveness of nupercaine hydrochloride and phenobarbital sodium for the suppression of ventricular tachycardia associated with acute myocardial infarction. They have had no deaths in 25 cases. On the other hand, death has occurred in some cases in which quinidine or pronestyl were used. They note that nupercaine given alone results in vomiting and convulsions so that phenobarbital is also necessary.

Some miscellaneous publications are interesting. Van Bogaert (42) described the electrophysiology of experimental ventricular extrasystoles. He pointed out that the excitation gives rise to vectors in all directions but that the vectors oblique or parallel to the ventricular wall are the efficient ones. Palmer (43) studied the isolated U wave negativity in the record; the mechanism is unexplained, but he considers it to be always pathological. Donzelot *et al.* (44) studied the effects of changes of posture on the QRS complex in the precordial leads.

#### EXTRINSIC INNERVATION: EXTRACARDIAC ARRHYTHMIAS

For study of tachycardia Odier (45) described an apparatus enabling direct measurement and recording of the cardiac rhythm. Blaizot (46) described a cardi tachometer for small animals (particularly the rat), by which heart frequency can be recorded without immobilization of the animal.

Supraventricular tachycardia complicating surgical procedures has been studied by Rogers *et al.* (47). They found 54 arrhythmias in 28,000 surgical procedures. Furman & Geiger (48) suggest the use of cholinergic drugs in paroxysmal supraventricular tachycardia. Neostigmine plus methacholine chloride resulted in two improvements but one death. Mazzei & Israel (49) recorded 25 cases of paroxysmal supraventricular tachycardia with atrioventricular block.

As usual, there are many studies of the effect of the nervous system on cardiac excitability. Hoffman *et al.* (50) consider the effect of vagal stimulation. Rapid vagal stimulation (20 per sec.) does not modify the "diastolic threshold." Greenberg & Lambeth (51) studied the response of the denervated heart to acetylcholine and epinephrine. Contrary to the law of denervation of the heart, the muscle is not hypersensitive to acetylcholine or to epinephrine, but acetylcholine does not slow the rhythm. In a similar study Hoffman and co-workers (52) have concluded that if the vagi are degenerated the negative chronotropic action of acetylcholine is increased. Nathanson & Miller (53) discussed the action of norepinephrine on the rhythmic function of the heart. Some clinical observations of thermoreceptive cardiac reflexes have been reported by Frank *et al.* (54). Immersion of the legs in cold water gives tachycardia and an increased amplitude of electrocardiograph deflections. The authors believe the experiment confirms the existence of specific thermoreceptive peripheral reflex mechanisms acting upon the heart, which may be responsible for some anomalies found in the electrocardiogram. Central regulation of the heart rate is discussed by Hoff (55). In the decerebrate state the neural imbalance resulting from unequal separation of the facilitating and suppressor systems in the brain stem gives rise to functional deafferentation of the suppressor system and consequent predominance of the facilitatory apparatus. This imbalance results in a marked bradycardia and decreased parasympathetic activity.

#### CARDIAC CATHETERIZATION

In hemodynamic studies catheterization is now as necessary as the electrocardiogram in the study of physiological disorders of the heart. Accidents during catheterization have been reported by a number of investigators. Hebert *et al.* (56) have had seven mortalities in the course of 1250 catheterizations. In one case the catheter penetrated into the pericardial cavity, without, however, any ill consequences for the patient [Stern *et al.* (57)]. Episcopo (58) shows that in 95 per cent of 40 catheterizations an arrhythmia appeared which usually was caused by contact of the tip of the catheter with the heart wall. Sometimes the arrhythmias are severe (supraventricular tachycardia, atrial fibrillation, transient atrioventricular block, or right bundle branch block). Sancetta *et al.* (59) described a case with traumatization of veins and subendocardial tissues of the right atrium but no myocardial damage. On the other hand, Edwards and co-workers (60) made a pathological study of hearts previously catheterized in 28 patients. There was one death during catheterization. The necropsy did not show any lesions which could

be attributed to the procedure. In only two cases were there any lesions: one small focus of hemorrhage in the right atrium, and a fibrinous deposit on the intimal surface of the pulmonary trunk; no pulmonary infarction was noted after wedging the tip of the catheter in a small pulmonary artery for purposes of the recording of "pulmonary capillary pressure" and withdrawing blood samples therefrom.

In important studies by Scebat *et al.* (61) and Lenègre *et al.* (62) the cardiac output, blood gases, and pressures (particularly capillary pressures) were investigated in different types of cardiac diseases. In agreement with previous reports they showed that the cardiac output is normal if the cardiac insufficiency is not marked, but if there is global cardiac insufficiency there is also a drop in cardiac output. With marked right ventricular failure a peripheral desaturation appears. In normal people during sustained effort the pulmonary capillary pressure does not change; usually, high pulmonary capillary pressure results from left ventricular insufficiency, mitral stenosis, or constrictive pericarditis. In their opinion the very high pulmonary capillary pressure is responsible for the pulmonary oedema. They pointed out the effects of increasing the output on the pulmonary system. The pulmonary capillary pressure is normal in chronic cor pulmonale or in congenital heart disease with high pulmonary arterial pressure. They insist upon the value of the gradient of pressure between the pulmonary artery and the capillaries.

A hemodynamic study of atrial fibrillation before and after conversion to normal rhythm has been made by Hansen and co-workers (63). They have shown in fourteen cases that the return to normal rhythm results in an increase of cardiac output and a diminution in the mean pulmonary arterial pressure and peripheral resistance. Metianu & Latscha (64) have recorded pressures through ventricular wall by puncture. They obtained very good curves, but in one case development of hemopericardium necessitated a surgical procedure.

#### ABNORMAL VENOUS RETURN

Brecher (65) studied the mechanism of venous flow under different respiratory conditions. At the beginning of a deep forced inspiration the extrathoracic veins empty a portion of their contents into the thoracic vein (depleting stage). Thus at the end of a deep inspiration these veins are completely collapsed. The same author (66) found that during inspiration venous collapse does not occur at one distinct point of entry into the chest but involves a more or less extensive segment of the extrathoracic vein. According to Girling (67) critical closing pressure in the arterioles is not explained by the positive pressure in the peripheral veins. Venous pressure during walking has been registered by Decamp & Witz (68). They compared a group of pressure curves from normal people with those from patients who have had phlebitis. The venous return is changed in the presence of atrial septal defects. Pedersen and Warburg (69) showed that the speed of the pulmonary circulation is doubled in patients with septal defects and that the diastolic filling pressure is increased.

## CONSTRUCTIVE PERICARDITIS

Experimental constrictive pericarditis has been produced by Boucek *et al.* (70, 71) and Isaacs, Carter & Holler (72). Constriction of the right atrium has no effect and the most important thing is constriction of the left ventricle. Accordingly, it is important to liberate both ventricles during surgical treatment. Yu *et al.* (73), Sawyer *et al.* (74), Thorniaire *et al.* (75), and McKusick (76) have studied this condition in man. The pressure curves of the right ventricle are usually considered to be characteristic of constrictive pericarditis. However, Hetzel *et al.* (77) have reported the same pattern in a case of amyloid disease of the heart and in a case of idiopathic heart failure. The pressure in the right ventricle at the end of diastole is exceedingly high so that the mean right atrial pressure has to be still higher in order to maintain positive gradient between these two chambers. Further, there is always an elevation of pulmonary capillary pressure which indicates a predominant involvement of the left ventricle. Usually, the stroke volume and cardiac output are low. After operation, myocardial atrophy, myocardial fibrosis, and incomplete relief of both ventricles may all play a role in the slow and incomplete return to normal dynamics, and so the objective of surgery is to release both ventricles. There is no reason for attempting a freeing of great veins or atria; possibly early use of antibiotics in acute tubercular pericarditis may minimize myocardial fibrosis and permit the achievement of better results. McKusick (78) made electrocardiographic study of constrictive pericarditis and obtained the same results. In some cases acute benign pericarditis (79, 80) can be responsible for subsequent constrictive pericarditis.

## CONGENITAL MALFORMATIONS

McCord & Blount (81) have carried out an excellent study of the hemodynamics of tricuspid valve disease. They had four patients with tricuspid regurgitation. The characteristic shown by the one with severe organic tricuspid disease was ventricularization of the right atrial pressure curve; the different shapes of the pressure curves permit differentiation of organic from functional regurgitation. In their view the ventricular pressure curve in patients with organic tricuspid disease is similar to that in constrictive pericarditis.

Ebstein's malformation has been described by Broadbent *et al.* (82) and by Edwards (83). In the latter paper four cases of Ebstein's disease were recorded, in each of which interatrial communication was present; in each of two a true atrial septal defect was present; in each of the other two, a patent ovale. Chiche (84) in a paper describing 14 cases of tricuspid atresia found four types of malformations: (a) interventricular septal defects with normal pulmonary circulation; (b) pulmonary atresia without interventricular septal defect (six cases); (c) the same as (b) plus transposition of the great vessels; (d) the same plus pulmonary stenosis. In the author's opinion the first, second, and fourth facts are amenable to surgical treatment.

A hemodynamic study of tricuspid stenosis has been carried out by Ferrer *et al.* (85). They studied two cases, one of which came to autopsy. They insist

that there is a pressure curve characteristic of tricuspid stenosis: the diastolic pressure in the right atrium is higher than the diastolic pressure in the right ventricle. They also made measurements of the stenosed tricuspid valve area and discussed the different procedures for making such measurements. Swan & Wood (86) have localized cardiac defects by recording dye dilution curves after injection of T1824 into multiple sites in the heart and great vessels during cardiac catheterization. In most cases of cyanotic heart disease this procedure gives a relatively high degree of certainty. Four cases of Lutembacher's syndrome have been recorded by Schopf (87) and Stiefel (88), two of which were autopsied; one showed a rheumatic stenosis and the other congenital stenosis of the mitral valve. Denolin *et al.* (89) report a case of interatrial septal defect with high pulmonary hypertension; they did not stress in the paper the possibility of Eisenmenger's syndrome.

Cardiac catheterization has been employed by Cosby (90), Neissel (91), and Bailey *et al.* (92) in the study of interatrial septal defects. The prognosis is variable and there is no medical treatment. A new technic of atrio-septopexy is described which involves suturing the right atrial wall to the margin of the defect, aided by a finger placed in the right atrium through the appendage. One patient with complete obliteration of the shunt and relief of symptoms is recorded. In this connection we are not forgetting the unpublished case of Gibbon who operated on a seventeen year old girl using an artificial heart with very good results.

#### PULMONARY CIRCULATION

Barger *et al.* (93) have studied experimentally in dogs the relation of valvular lesions and of exercise to atrial pressure, work tolerance, and development of chronic congestive failure. Pulmonary insufficiency gives no effects; pulmonary stenosis causes a slight elevation of pressure in the right atrium; the same results appear in tricuspid insufficiency. Pulmonary and mitral stenosis plus tricuspid insufficiency result in an enlarged right heart with high pressure in the right atrium and dilatation of the vein.

*Pulmonary stenosis.*—The role of pulmonary stenosis in the production of chronic cyanosis has been described by Selzer & Carnes (94). Pulmonary stenosis without intracardiac communication does not produce cyanosis, except when there is failure. In the presence of pulmonary stenosis and patent foramen ovale the chronic cyanosis results from the right to left shunt. Connolly *et al.* (95) have found that during operative relief of pulmonary stenosis there is a fall in right ventricular pressure when the orifice is very well dilated.

McCoid *et al.* (96) described the characteristics of the right atrial pressure wave associated with right ventricular hypertension, and Pannier *et al.* (97) studied eight cases of isolated pulmonary stenosis in which the ether test was negative. The results of the Blalock procedure for relief of pulmonary stenosis have been studied by Bret (98) and Joly *et al.* (99).

Some very special cases of pulmonary stenosis have been investigated by Broadbent (100) and by Provenzale (101). Ten cases, five with atrial



septal defects and five with ventricular septal defect, were described in which pulmonary arterial pressure and flow were normal or increased. With a ventricular septal defect the systolic pressure in the right ventricle is not different from the systemic pressure. This is a diagnostic point differentiating this condition from pulmonary stenosis plus atrial septal defect in which these pressures are quite different. Carlotti *et al.* (102) studied the electrocardiogram in 35 cases of isolated intracardiac defects; they showed that there is no relation between the hemodynamic disorder and the electrocardiogram.

A very important aspect of the physiopathological study of the pulmonary circulation is now to know the real pressure in the left atrium. A theoretical problem concerning the morphology of the pulmonary capillary pressure is discussed by Van Bogaert *et al.* (103); experimenting on the dog, they showed the value of the pulse registered in the capillary bed. Connolly *et al.* (104) have considered the morphology of the pulmonary capillary curve before, during, and after valvulotomy, and they stress the value of the capillary pressure in relation to the value of the pressure in the left atrium; they also described the morphology of this curve in the presence of mitral regurgitation. In relation to the same problem Aranjó & Lukas (105) have discussed the interrelation between pulmonary capillary pressure, blood flow, and valve size in mitral stenosis. Others try to record pressure in the left atrium by direct measurement or indirect techniques. Moniz de Bettencourt *et al.* (106) tried to use tomography of the pulmonary veins. Van Den Heuvel & Heymans (107) registered pressure curves of the left atrium through the esophagus. Facquet *et al.* (108) and Allison & Linden (109) registered the left atrial pressure by a needle passed into the bronchus with the use of a bronchoscope. A study of the pulmonary vascular bed in the dog through determination of the pressure volume characteristics has been made by Sarnoff & Berglund (110). Richards (111) studied lung volumes in hyperkinetic states and in patients with hyperthyroidism and anoxemia.

*Pulmonary vascular resistance.*—In anesthetized dogs this factor has been studied by Haddy & Campbell (112). Halmagyi (113) shows the role of the nervous system in the maintenance of pulmonary arterial hypertension in heart failure. On the basis of findings in 46 patients he discussed the influence of neurogenic vasoconstrictor tonus in determining pulmonary resistance and pulmonary arterial pressure. According to Hall (114) anoxia affects pulmonary vascular resistance through a postarteriolar effect. Peters & Roos (115) discussed the effect of nitrogen breathing on pulmonary blood flow. Fishman *et al.* (116) have shown that, after a steady state is achieved, anoxia causes no change in cardiac output although there is a slight elevation of pulmonary arterial pressure. According to Meriel *et al.* (117) hydergine has no vasomotor effect in the pulmonary bed.

*Pulmonary edema.*—Pierach & Stotz (118) showed that novocainization of the right stellate ganglion causes death in cases with acute edema of the lung. Goldmann & Luisada (119) discussed the value of the alcohol-oxygen vapor therapy of pulmonary edema in 50 attacks.

*Mitral stenosis.*—In an experimental study Haddy *et al.* (120) showed



that cardiac function in experimental mitral stenosis in the dog is not exactly comparable to that in the human. Van Bogaert *et al.* (121) discussed the pathogenesis of pulmonary arterial hypertension after ligation of the pulmonary vein. In the absence of anoxia there is a vague reflect of arteriolar origin which gives rise to a durable hypertension. From the clinical point of view, Soulié *et al.* (122) and others (123 to 129) have discussed the indications for commissurotomy for the relief of mitral stenosis. The results are a function of the different types of mitral stenosis with or without regurgitation. Levine & Love (130) have shown that there are some very rare cases of mitral stenosis with symptoms of pulmonary hypertension and a high pulmonary capillary pressure but without any diastolic cardiac murmur.

A large number of papers deal with the problem of hemodynamics in mitral stenosis before and after commissurotomy. Carloti *et al.* (131) discussed two types of mitral stenosis, one with a low pressure gradient between the pulmonary artery and the pulmonary capillaries, the other with a high gradient of pressure, and they showed that the differences between these types bear some relation to the clinical aspects. Circulatory dynamics in this condition before and after operation have also been studied by Werkö *et al.* (133) and others (132, 134 to 140). Soulié *et al.* (141) are attempting to determine the relation between the hemodynamics and the anatomical lesion in mitral stenosis. Several facts show a close relation. Blocking of pulmonary alveolar capillaries in the presence of a normal peripheral saturation seems to be due to the exclusion of the circulation from the pulmonary regions most altered; the authors thus explain the high pulmonary resistance and the prognosis of this type of mitral stenosis. Clinical and hemodynamic studies have also been made before and after commissurotomy by various authors (142 to 146). There is a close relation between the clinical results of mitral commissurotomy and the results of physical examination, of electrocardiographic study, and of the results obtained by cardiac catheterization. Cases of tumors of the left atrium which resemble mitral stenosis have been studied by Desbaillets *et al.* (147) and Block *et al.* (148).

*Mitral insufficiency.*—All authors discussing the problem of commissurotomy for relief of mitral stenosis are now very much interested in making the diagnosis of mitral insufficiency. Burchell & Edwards (149), Brigden & Leatham (150), and Soulié *et al.* (151) consider the different problems arising in this connection. They stress the importance of fluoroscopy and the electrocardiographic changes in making this diagnosis.

*Pulmonary hypertension.*—Werkö & Eliasch (152) and Howarth & Lowe (153) discussed the mechanism of primary pulmonary hypertension. There are a few publications on chronic cor pulmonale by Fowler *et al.* (154), Lewis *et al.* (155), Taquini (156), and Arrillaga & de Soldati (157). In chronic lung disease with polycythemia and congestive heart failure, correction of the polycythemia causes the arterial unsaturation to become more severe, and it seems that the blood viscosity plays a role in the increase of pulmonary resistance.

A number of papers, particularly from Europe, deal with the problem of

artificial heart-lung apparatus [Thomas (158), Thomas & Alfsen-Blanc (159, 160), Vayssé *et al.* (161), and Dubbelman (162)]. It appears that a factor exists through which oxygenation for a given oxygen pressure in the alveoli raises the saturation of the blood when all mechanical conditions in the artificial heart-lung remain constant. According to the studies now being made, it seems that this enzyme, globin oxydase, plays an important role (André Thomas, Alfsen-Blanc).

#### THE HEART AS A PUMP

The study of the dynamics of the circulation is still proceeding intensively. Lasser *et al.* (163) used an oximetrically determined circulation time from the right ventricle to the ear in congenital heart disease; with a catheter in place they injected Evans blue into the vein and studied the time of arrival of the dye in the ear by means of a Millikan oxymeter. Frieden & Schaffer (164) described a simple method for the repeated determination of cardiac output in the anesthetized dog, using an indwelling cardiac catheter. Cathcart *et al.* (165) compared the cardiac output determined by the ballistocardiograph and by the direct Fick method; they find a poor correlation. Pritchard *et al.* (166) determine cardiac output by a continuous recording system using human serum iodinated with  $I^{131}$ . The values obtained are  $\pm 8$  per cent of those obtained by the Fick method. Grossman *et al.* (167) used a method for determining cardiac output by the direct Fick principle without gas analysis. With a double lumen catheter they injected para-amino-hippuric acid into the pulmonary artery and took blood samples in the right ventricle. Opdyke (168) considered the pressure pulse contour method for calculating the cardiac stroke index. The basal cardiac output in relation to body composition with particular reference to obesity has been studied by Taylor *et al.* (169). The effect on the human third heart sound of variations in the rate of filling of the heart has been studied by Sloan & Wistart (170).

Berne & Levy (171) have investigated some physiological effects of an acute reduction in cardiac output on the denervated kidney. Elisberg *et al.* (172) have observed the effect of the Valsalva maneuver on circulation, and Stein (173), the tendency toward hypotension in left lateral recumbency.

#### BALLISTOCARDIOGRAPHY

General reviews on the problem of ballistocardiography have been written by Scarborough *et al.* (174), Gubner *et al.* (175), Starr (176), and Rappoport *et al.* (177). Thompson *et al.* (178) give a description of the normal ballistocardiograph; as a result of a comparison between the electrocardiogram, the ballistocardiogram, and the phonocardiogram, they emphasize the parallelism between the ballistocardiogram and the phonocardiogram. In detail, the F wave appears at the same time as the atrial sound in the phonocardiogram between the P and Q waves of the electrocardiogram. The G wave is closely related to the third component of the first heart sound. The H wave corresponds to the ventricular ejection phase and to the acceleration of blood in the great vessels. The I wave appears at the end of the maximum ejection

phase. The J wave corresponds to the vibrations at the end of systole. The K wave appears with the closing of semilunar valves. The L wave occurs at the time of the opening of the atrioventricular valves. The N wave appears at the same time as the third heart sound and coincides with the peak of the rapid inflow phase of the ventricles. Reeves *et al.* (179) describe a method for calibration of the direct ballistocardiogram. Brown *et al.* (180) studied the correlation of the ballistocardiogram with work performance and the energy which cardiac patients have for rehabilitation programs. The normal form of the ballistocardiogram is discussed in several publications, particularly in that by Scarborough *et al.* (181) who give 60 variations in the form of the normal ballistocardiogram. Studies of the ballistocardiogram in various heart diseases include the following: Davis (182) on mitral stenosis, Roehm *et al.* (183) on hypertension including the results of drug administration, Scarborough *et al.* (184) on coronary heart disease, and Jones (185) on atherosclerotic heart disease with and without congestive failure.

#### CORONARY CIRCULATION

Weinbury & Green (186) have studied the nervous and humoral control of the coronary circulation. The stimulation of sympathetic nerves increases the coronary flow as do epinephrine, histamine, and acetylcholine. Changes in flow and in pressure are parallel; the autonomic nervous system does not seem to exert a vasoconstrictor control. The effect of vasomotor drugs and of anemia on interarterial coronary anastomoses has been studied by Zoll & Norman (187). Spritzler *et al.* (188) seem to have demonstrated the existence of spasm; this is the first time that such a spasm has been shown. Gunther & Landis (189) have studied the flow-pressure relationship in quiescent and beating turtle hearts. The quantitative relationship between pressure and flow in the coronary system of the dog heart has been investigated by Osher (190), who found that pressure and flow are mathematically related. Winder & Thomas (191) have studied rabbit hearts with special reference to the perfusion pressure after papaverine vasodilatation. Waser & Hunzniger (192) have studied the human coronary circulation using  $\text{Na}^{24}\text{Cl}$ . With an increase in heart rate from 60 to 110 there is a slight increase of arterial pressure; the coronary circulation time increases as does the relative coronary flow. Eckstein *et al.* (193) have shown the acute effects of elevated coronary sinus pressure; in normal subjects they found a slight myocardial anoxia with characteristic electrocardiographic changes and a fall in cardiac output. After coronary ligation, coronary sinus arterialization is beneficial.

In an extensive study Freedberg & Riseman (194) have reported observations on the carotid sinus reflex in angina; they point out that pressure on the sinus causes the pain to disappear not by modifying the coronary circulation but by blocking the reflex pathways for pain. The exercise tests have been studied by Scherf & Schaffner (195); they have shown that for an abnormal electrocardiogram to appear during exercise it is necessary to have an ST depression less than 2 mm. Lombardo *et al.* (196) demonstrated the effect of exercise on coronary blood flow and myocardial oxygen consumption in man

by catheterization of the coronary sinus and the nitrous oxide method. They point out that moderate exercise increases the coronary flow without changing the oxygen extraction. Left ventricular work is increased more than the oxygen consumption, thus the left ventricular efficiency is increased in normal subjects. In patients with left ventricular failure they obtained contrary results. Evrard (197) applied the step-test to the selection and medical control of flying personnel. Turner & Morton (198) used a 10 min. anoxia test which they consider a good test for coronary insufficiency if the ST segment is depressed by more than 2 mm. in V4. The hypoxia test for coronary insufficiency controlled by a Millikan oximeter is suggested by Tewell & Pritchard (199). The smoking test has been studied by Fabre *et al.* (200); they showed that there are some individual variations. Mann & Burchell (201) point out that the appearance of premature ventricular contractions during exercise in patients with coronary insufficiency is a test of value in selecting patients with angina. The exercise test has also been applied to the study of bundle branch block by Feil & Brofman (202). Fabre (203) studied the effect of effort on pressure during the test. Talley *et al.* (204) used pentaerythritol tetranitrate in the treatment of angina pectoris with negative results.

#### MYOCARDIAL INFARCTION

Extensive studies of experimental infarction, usually in the dog, have been made by Agress (205), Levy & Fraenkel (206), Johnson *et al.* (207), and Hurlimann (208); these include reports on the effects of cortisone on the size of the experimental myocardial infarcts. Hahn *et al.* (209) produced revascularization of the heart following experimental infarction by arterialization of the coronary sinus. Von Wedel *et al.* (210) revascularized the heart in dogs by means of a pedicle skin flap. Selzer (211) has studied the hypotensive state following acute myocardial infarction in man; he distinguished four kinds of shock: immediate shock with a mild fall in arterial pressure; severe irreversible shock; shock from cardiac arrhythmia; and delayed shock due to cardiac failure. In his opinion the early shock is caused by a peripheral vasomotor reflex mechanism. The later shock in cardiac failure is irreversible. Experimenting in dogs, he (212) showed that the performance of the left ventricle is normal when a major branch of the coronary artery is ligated, but when two major arteries are ligated there is true shock with a massive acute infarct. Hellerstein *et al.* (213) treated the shock accompanying myocardial infarction with the pressor amine mephentermine, which is supposed to have a beneficial effect. The mortality in myocardial infarction has been estimated by Wooten & Kyser (214) in a study of 455 cases.

The problem of the electrocardiographic pattern in myocardial infarction is reviewed in papers by Papp & Shirley-Smith (215), Slapak (216), Osher & Wolff (217), Tulloch (218), Rodriguez *et al.* (219), and Wolff & Richman (220). Van Dooren & Boyadjian (222) reviewed 177 cases of "T1 less than T3" pattern. Phares *et al.* (221) studied the clinicopathology of 40 cases of cardiac aneurysm. Prinzmetal *et al.* (223) studied the intramural depolariza-

tion potentials in myocardial infarction. In direct leads from the infarct there are two types of QS deflection. In the first type the negative potentials of the ventricular cavities are transmitted. This type results from a large infarct without any intact muscular fibers. In the second type in which some myocardial fibers survive it appears that the QS wave arises from the epicardial fiber.

#### ANTICOAGULANT THERAPY

The physiological action of dicumarol has been studied by Quick *et al.* (224). Extensive studies for the evaluation of anticoagulant therapy have been made: (a) on myocardial infarction by Wright (225), Beaumont *et al.* (226, 229, 231), Feldman *et al.* (227), Russek *et al.* (228), and Zapfe & Sonnenberg (230); it seems that all authors agree on the value of anticoagulant therapy in all cases of myocardial infarct: it prevents peripheral embolism; it appears to reduce the mortality in that when carried out wisely it is without any danger for the patient; (b) on coronary insufficiency by Russek (232), Donzelot *et al.* (233), Rinzler (234), Grüner *et al.* (235), and Beaumont *et al.* (236); the results of anticoagulant therapy in this condition are differently interpreted by the authors, some finding 70 per cent improvement, others no beneficial effects at all; it appears that actually one cannot expect a good response to anticoagulant therapy in coronary insufficiency; (c) on congestive heart failure and thromboembolic diseases by Griffith *et al.* (237), Cloetens *et al.* (238) and Cosgriff (239); all of these authors agree on the possibility of thromboembolic complications in chronic congestive failure and on the necessity of prophylactic anticoagulant therapy which can be carried out without harm for the patient.

#### ELECTROLYTE METABOLISM, WATER METABOLISM, METABOLISM OF CARDIAC FAILURE

Radioactive  $P^{32}$  and  $I^{131}$  have been used by Berson *et al.* (240, 241) for the study of acute changes in blood volume; albumin tagged with  $I^{131}$  gives a good estimate of the circulating plasma volume. Danowski (242) has reported an extensive study of the electrolytes in congestive failure. There is sodium retention and defective action of the kidney in failure. A possible humoral influence is suggested and the necessity of studies at the cellular level emphasized. According to him one of the mechanisms operating in congestive failure results from changes of cellular function. In orthostatic hypotension the effects of posture on the renal excretion of sodium and chloride have been studied by Bachman & Youmans (243) who have shown that there is a fall in sodium excretion when the patient is standing up. The total body sodium, potassium, and nitrogen have been studied in rats made hypertensive by subtotal nephrectomy (244).

The effects of electrolyte changes on the electrocardiogram have been investigated by Parrish *et al.* (245), Butcher *et al.* (246), Merklen *et al.* (247), and Henderson (248). In isolated perfused hearts of dogs and turtles the electrocardiogram was recorded in the lumen and on the epicardium. Potassium

excess causes in both species increase in QRS complex height, depression of the ST segment, and an elevation of P and T waves; later diphasic or monophasic complexes develop. If both calcium and potassium are present in excess the QRS depression is reduced, but the ST segment is more depressed. If sodium is added partial reversal of the electrocardiographic changes from potassium excess occurs. If potassium is absent P-R increases, the QRS complex is more ample, and the ST segment is elevated (in the turtle). In dogs the same results appeared except that there is no change in the QRS complex. These results are consistent with the phenomena observed in the human heart.

Several papers by Weston *et al.* (249), Moyer *et al.* (250), and Cahen *et al.* (251) report the response to mercurial diuretics in cardiac failure. They stress the idea that adrenal cortical activity may contribute to resistance to the mercurials by increasing tubular reabsorption of sodium and that the distal tubular exchange mechanisms for conserving sodium may be responsible for the increased potassium excretion. The relation of mercurial diuretic administration to thrombosis was studied, and the conclusion was reached that there is no real danger of thrombosis during prolonged treatment with these substances.

Metabolic studies on the effects of administration of exchange resins to patients with cardiac failure have been made by Weston (252), Duncan (253), Greenman *et al.* (254), and de Gennes *et al.* (255). All of these authors favor the use of resins in the potassium cycle but they point out the danger of acidosis.

The renal excretion of radioactive digitoxin by human subjects with cardiac failure has been studied by Okita (256), who found 60 to 80 per cent in the urine. This is the first direct study of digitoxin excretion. Most of the  $C^{14}$  from the drug is eliminated as metabolic products, while only 6 to 10 per cent of the drug administered is excreted as unchanged digitoxin.

The effects of hexamethonium on certain manifestations of congestive failure have been studied by Kelly *et al.* (257). The drop in peripheral resistance increases the work of the heart and improves the state of the patient. Cournand (258) has given an account of the concept of cardiac failure in the light of recent physiological studies in man.

The cardiovascular dynamics, blood volumes, renal functions, and electrolyte excretions have been studied by Eichna (259) in the same patient with chronic congestive failure. The relation of the choline cycle to this condition has been discussed by Govier *et al.* (260) and the relation of cardiac failure to cardiac muscle by Bing & Taeschler (261). The alterations in liver function in chronic congestive heart failure have been considered by Evans (262).

There is always some discussion concerning edema formation, renal function, and the pressures in different parts of the organism. Katz & Stamler (263) and Peters (264) point out that there is no difference between the edema of cardiac insufficiency and that of acute nephritis.

According to Novack (265) there is no decrease in cerebral blood flow



in the absence of arteriosclerosis. Soloff *et al.* (266) have discussed the relationship of certain electrolytes of the serum, edema fluid, and urine in a case of intractable heart failure. Wilkinson *et al.* (267) discussed the cardiovascular adjustments and changes in renal blood flow in relation to the hypotensive agent. Strauss (268) believes that administration of an extract of veal heart gives good results in some patients with cardiac failure.

#### ELECTROCARDIOGRAPHY: MISCELLANEOUS

The spatial QRS loop in right ventricular hypertrophy has been studied by Fowler & Helm (269) with special reference to the initial component. Lipsett & Zinn (270) compared the anatomic and electrocardiographic findings in 73 patients with combined ventricular hypertrophy who came to necropsy. They stress the difficulty of diagnosis of right ventricular hypertrophy which can be recognized by rotational changes of the axis. Pagnoni & Goodwin (271) emphasized the same problem in the diagnosis of combined ventricular hypertrophy. Doyle (272) discussed the electrocardiographic changes in 75 hypertensive patients treated with methonium compounds; according to him the improvement in the electrocardiogram appears to be directly related to the degree of control of arterial pressure.

The electrocardiogram of levo- and dextrocardia has been discussed by Campbell & Reynolds (273), Moscovitz *et al.* (274), and Burchell & Pugh (275). If there is dextrocardia with situs inversus and cyanosis, the P1 is inverted; if there is an isolated dextrocardia with cyanosis the P1 is nearly always positive; if there is an isolated levocardia, the P1 is always inverted.

The electrocardiograms of normal subjects subjected to compressed air and that of airmen in flight have been studied by Hagen & Sensing (276) and Glatt (277). They usually show tachycardia and a change of the rhythm.

Reynolds (278) has presented the results of his study of the electrocardiographic changes during angiocardiology from a prognostic point of view and has shown that, when there appears an arrhythmia during the test under anesthesia the procedure must be discontinued because some deaths have occurred under these circumstances.

According to Grewin *et al.* (279) iodine therapy in thyrotoxic crises of the cardiac type gives good results. The electrocardiographic mirror pattern has been studied by Simonson *et al.* (280, 281, 282) in 17 normal and 37 cardiac patients. They emphasize that true mirror patterns are not rare. Shearn & Rytand (283) have studied intermittent bundle branch block. In their view there is no difference between intermittent bundle branch block and complete bundle branch block, but they insist upon the notion of a critical pulse rate. Lape & Maison (284) have described a case of resuscitation and survival in dogs following electrically induced ventricular fibrillation.

#### DRUG ACTION

*Autonomic drugs.*—Chunney (285) described the monophasic action potential of atrial muscle during epinephrine action; he found that the atrial muscle contracts more forcefully, but that vagal stimulation decreases the



amplitude and duration of the monophasic action potential of the atrial muscle. Brofman *et al.* (286) have studied mephentermine, and effective pressor amine with norepinephrine-like action. It causes no change in the rate, rhythm, or irritability of the heart and so appears to have no direct action on the heart; no side effects occurred. Swan (287) described the action of epinephrine and norepinephrine on the human circulation, while Laszt & Krueger (288) considered the circulatory effects of these substances in comparative experiments. Garb (289) investigated the action of these agents on mammalian heart muscle and demonstrated the inability of nitrates to block their effects. Opdyke (290) studied the effects of changes in initial tension, initial volume and epinephrine on the ventricular relaxation process. He concluded that ventricular filling is not disturbed.

*Metabolic substrates.*—Matsuoka (291) has investigated the ability of various substrates to restore the amplitude of contraction in rat ventricle strips depleted of substrate.

*Digitalis.*—Woodbury & Hecht (292) have shown that cardiac glycosides alter the behavior of single ventricular fibers. The action of crystalline digitalin (Digitoxin) and strophanthin has been studied by Hockerts (293) through measurement of coronary arterial pressure-flow relations. Gray *et al.* (294) have shown the modifications of the circulation produced by lanatoside C in chronic pulmonary diseases. Gold *et al.* (295) point out the differences in the ratio of cardiac to emetic action in oral and parenteral digitalization. The results of the study show that if the gastrointestinal tract is bypassed through use of the intravenous or intramuscular route more action on the heart can be obtained without gastrointestinal disturbances. Hejtmancik & Herrman (296) recommend a dose of 0.5 mg. digitalin per day for average digitalization. The effect of digitalis on the normal electrocardiogram has again been reviewed by Tiliakos (297) who reached the same results as previously.

*Quinidine and quinidine-like.*—The effects of procaine amide and quinidine on the human heart have been studied extensively by Lequime *et al.* (298), Zapata-Diaz *et al.* (299), Miller *et al.* (300), Lucas & Short (301), Schack *et al.* (302), and Cutts & Rappoport (303). In human beings rapid injection of pronestyl gives a transitory drop in arterial pressure, an increase in cardiac output, and at the same time an increase in the excitability of the heart, and slows induction rate in both atrium and ventricle. If some arrhythmia appears during the treatment of cardiac failure because of overdosage with digitalis, procaine can abolish the extrasystole, but it is still dangerous, and according to Miller it is very dangerous in heart block. Pronestyl is of some value in stopping paroxysmal ventricular tachycardia but has no prophylactic effect in preventing the arrhythmia caused by mechanical irritation of the heart. Schack *et al.* (302) were unable to find any effect of procaine amide on arrhythmias or supraventricular tachycardia. Cutts & Rappoport (303) find the routine use of quinidine in acute myocardial infarction interesting but state that in very high doses it can result in sudden death.

*Miscellaneous drugs.*—The alkaloids of *veratrum viride*, according to

Krayer (304), exert an active blocking effect on the cardio-accelerator mechanism. In some cases in which large doses of central nervous system stimulants were used, Bennett & Walker (305) found cardiac arrhythmia. Kuhns (306) has tried to stop some cardiac arrhythmias with Hydergin and obtained very good results in atrial fibrillation. In a case of beri-beri heart disease Lahey *et al.* (307) demonstrated the very acute effect of thiamine. Veratrum viride products given intravenously produce a rather prolonged decrease in arterial pressure according to Mills & Moger (308). Moger (309) and Riven (311) found 1-hydrazinophthalazine (Hydrallazine) to reduce the arterial pressure through central vagodepressive action. Similar results were obtained by Balake & Williams (310) with B-alkylamine. Sokolow & Schottstaedt (312) consider as most effective a mixture of small doses of hexamethonium and Hydrallazine. Hobler *et al.* (313) favor the treatment of hypertension with protoveratrine, which reduces the arterial pressure more than does veratrum viride. Wilkins (314) has written an extensive review of new drugs used in the treatment of arterial hypertension. Various types of drugs are now available for long-term clinical trial. No one is as yet ideal, but a number are effective particularly in combination. Apoverine, veratrum viride and Rauwolfia serpentina appear to be safe and well tolerated when given in small doses over long periods of time; they give a gradual reduction of pressure and subjective and objective improvement without side effects. Only long-term studies will show whether such agents prolong the lives of hypertensive patients.

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## THE KIDNEY<sup>1,2</sup>

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### GLOMERULAR FILTRATION

The measurement of the rate of glomerular filtration (GFR) remains fundamental to evaluation of most of the quantitative aspects of renal mechanisms. For a few purposes, particularly for the clinical evaluation of renal function, there is probably a place for approximation methods. But where the aim is the measurement of tubular transport or assessment of the role of changes in filtration in the modification of excretion rates there is no substitute for the most rigorous technique. The most careful technique is, under many circumstances, especially with low or changing urine flows, none too sharp a tool, but to dull it further by the use of rapidly changing plasma concentrations of the reference substance or the employment of reference substances whose mode of excretion is variable and uncertain seems to militate against the acquisition of critical data.

The question of the independence of inulin clearance from its plasma concentration in man has been re-examined by Kennedy & Kleh (1). The inulin clearance was measured successively at each of three stable concentrations in the plasma ranging from 3 to 175 mg. per cent. Careful statistical analysis of the data failed to suggest any departure from direct proportionality between excretion rate and plasma concentration. They found no tendency for a lowering of clearance at low plasma concentration such as was described by Ferguson *et al.* (2). It is suggested that the use of falling plasma levels in the latter study may account for the different findings. Results similar to those of Kennedy & Kleh were obtained by Mattar and associates (3) in a smaller series.

Because of its normal presence at stable concentration in the plasma,

<sup>1</sup> This review covers the period from that of the last review on The Kidney (May, 1951) to approximately May 1, 1953. Much of the material covered by the review of water metabolism (Volume 15, 1953) and all papers concerned chiefly with phosphate excretion and the parathyroids have been omitted. In addition, because of limitations of space, material published only in abstract form has been included only when particularly pertinent to the discussion.

<sup>2</sup> The following abbreviations are used in this chapter: ACTH (adrenocorticotropin); ADH (antidiuretic hormone); BP (blood pressure); C<sub>B</sub> (barbital clearance); C<sub>CR</sub> (creatinine clearance); C<sub>IN</sub> (inulin clearance); C<sub>M</sub> (mannitol clearance); C<sub>PAH</sub> (*p*-aminohippurate clearance); C<sub>U</sub> (urate clearance); DCA (desoxycorticosterone); ECF (extracellular fluid); GFR (glomerular filtration rate); IP (interstitial pressure); PAH (*p*-aminohippurate); PSP (phenolsulphonphthalein); RBF (renal blood flow); RPF (renal plasma flow); T<sub>m</sub> (tubular maximum); 6063 (2-acetyl-amino-1,3,4-thiadiazole-5-sulfonamide).

endogenous creatinine would have characteristics highly desirable for measurement of glomerular filtration in man were it excreted by filtration only. Unfortunately there is little reason for believing the latter to be the case either for the heterogeneous "creatinine chromogen" or the "specific" creatinine determined by enzymatic digestion or by the use of Lloyd's reagent. Mattar *et al.* (3) used the latter procedure to compare the clearances of creatinine and inulin in a group of children with normal and diseased kidneys. In the normal group the ratio  $C_{CR}/C_{IN}$  averaged 1.03 with a standard deviation of 0.11. In the group with low  $C_{IN}$  there was a progressive elevation of the ratio to values as high as 2.2. The latter was attributed to tubular secretion of creatinine in the presence of disease. Since it seems unlikely that new functions are acquired under such circumstances, it seems probable that the coincidence of the average  $C_{CR}$  and  $C_{IN}$  in the normal is fortuitous. In any case the wide scatter of the ratios in the normal give no confidence in the validity of the  $C_{CR}$  in the individual instance. Similar results were obtained by Miller and associates (4) in applying the enzymatic method in adults with renal disease. Results with this procedure did not differ greatly from those obtained using total creatinine chromogen with the  $C_{CR}/C_{IN}$  ranging from 0.56 to 1.64 (total chromogen) and from 0.82 to 1.71 ("specific" creatinine). In both instances only one ratio in nine fell between 0.9 and 1.1. In the face of these findings and the earlier results of other investigations, it is difficult to explain the data of Haugen & Blegen (5) who, using Lloyd's reagent, find  $C_{CR}/C_{IN}$  to average 1.01,  $\sigma = .07$ , in normal and diseased patients. Sources of error in the determination of endogenous creatinine are considered by Lauson (6). The clearance of allantoin has never found wide use in the measurement of filtration in man, and its usefulness seems doubtful in view of the findings of Miller *et al.* (7) that in patients with renal disease the ratio of allantoin clearance to  $C_{IN}$  ranged from 0.64 to 1.03 with only 3 of 9 close to 1.0. The continued introduction of new procedures for the determination of inulin in plasma and urine (8, 9) attests to the frequency with which difficulties are encountered with available methods.

In the dog, the identity of  $C_{CR}$  and  $C_{IN}$  has long been accepted. Further confirmation is offered by the work of Selkurt (10) who finds  $C_{CR}/C_{IN} = 1.01 \pm .07$  in dogs subjected to marked anoxia. The clearance of creatinine in the dog has been re-examined by Kennedy *et al.* (11) who find that when the recovery of creatinine from plasma is complete (a situation not obtained when tungstate precipitation was used), the  $C_{CR}/C_{IN}$  averages 0.94. The deficit in creatinine clearance is apparently attributable to binding of creatinine on plasma protein to an equivalent extent, and  $C_{CR}/C_{IN}$  is not affected by diuretics, inhibitors of transport, or changes in plasma creatinine concentration. Although the validity of  $C_{CR}$  as a measure of GFR<sup>2</sup> would not be affected if account is taken of protein binding and recovery from plasma, it is not clear why the discrepancy was not revealed in earlier work.

Sapirstein *et al.* (12) affirm the validity of the estimate of GFR from the decay of plasma mannitol concentration with time following single intra-

venous injection in the dog. The finding of essential identity of  $C_{CR}$  and  $C_M^2$  is not in agreement with other recent work.

In the rat, the work of Fingl (13) confirms that of Martel *et al.* (14) in indicating secretion of creatinine by the tubules. The  $C_{CR}$  undergoes self-depression on elevation of the plasma concentration, and secretion is apparently inhibited by Benemid (see p. 274) and by PAH.<sup>3</sup> In rabbits, Effersoe (15) finds  $C_{IN} = C_{CR} = C_{THIOSULFATE}$  under normal conditions, but that when sodium benzoate is administered  $C_{CR} < C_{THIOSULFATE} < C_{IN}$ . The change is attributed to "intoxication of the tubules causing pathological reabsorption of creatinine and thiosulfate."

In micropuncture studies of *Necturus*, Bott (16) confirms the identity of creatinine and inulin clearances, finding identical tubule fluid/serum ratios throughout the length of the tubules.

Chinard (17) re-examines the theory of the formation of glomerular filtrate and concludes that diffusion rather than filtration (as a result of bulk flow under pressure) is the mechanism involved. Since, by the definition of bulk filtration which is used, there can be no effect of the influence of protein on activity of water in capillaries (usually referred to as oncotic pressure), the distinction seems to be in part one of definition. The formulation takes no account of the effect of solvent movement on the movement of solute (17a). Calculation of the glomerular surface area through which substances pass, based on the diffusion hypothesis and a thermodynamic formulation, yields a value estimated to correspond to the whole capillary surface. Since no separation of substances of diffusibility equal to or greater than inulin is effected, no effects on the measurement of the filtration of such substances would be implied by this concept.

The permeability of glomerular capillaries has been assessed in a number of studies. Beattie & Corcoran (18) report studies of a fructosan (molecular weight 5400 to 9000) from Italian rye grass, finding a clearance lower than  $C_{CR}$  in the dog and falling with time as the smaller molecules are preferentially lost in the urine. In normal man clearance of the fructosan was at about the level of GFR but in the presence of proteinuria clearance of the fructosan fell, suggesting an overall reduction of glomerular permeability. Qualitatively similar results were obtained by Beattie & Bell (19) with several fructosans from other sources. Using dextran in patients with proteinuria, Wallenius (20) finds a rise in the clearance relative to  $C_{IN}$  and the excretion of larger dextran molecules than in the normal, a result with the opposite implications from that of Beattie & Corcoran (18). For dextran of the particular degree of branching used in their studies, Grönwall *et al.* (21) find a rather sharp cutoff for urinary excretion at molecules of M wt. of about 45,000. McDonald *et al.* (22) find the relationship between hemoglobin (Hb) concentration in plasma and Hb excretion in man such as to suggest that 10 to 16 per cent of the area available to the passage of inulin is available for Hb. Lambert *et al.* (23) find  $C_{Hb}$  in dogs less depressed by massive doses of epinephrine than  $C_{CR}$  and attribute this to continued dissipation

of the concentration gradient for Hb from capillary to glomerular space when reduction in filtration pressure has reduced the filtration of creatinine. Chinard *et al.* (24) find the clearance of T1824 a useful substitute for the immunochemical determination of albumin clearance in the study of proteinuria.

The problem of the continuous or intermittent nature of glomerular activity has come in for re-examination. In the frog, the presence of intermittent activity has been generally accepted, but re-examination by Grafflin & Bagley (25) failed to reveal significant intermittence in urethanized frogs, and the authors conclude that it is not a characteristic feature "under normal physiological conditions." On the other hand, continuous activity of the glomeruli in dog and man has been considered the rule. This concept has also been questioned, largely as a result of the work of Handley & Moyer (26 to 29) who have found in dogs more or less proportional changes in  $C_{CR}$ , RPF,<sup>2</sup> and  $Tm_G$  in a number of experimental circumstances. This is contrary to earlier work and to the findings of Thompson, Barrett & Pitts (30) who found no change in  $Tm_G$  when  $C_{CR}$  was reduced as much as 60 per cent by bleeding, inflation of a balloon in the aorta, or dehydration with mercurial diuretics or when  $C_{CR}$  was increased by saline infusion. When  $C_{CR}$  was reduced to 40 per cent or less of control values,  $Tm_G$  showed some fall, but under these conditions the filtered load of glucose approached or fell short of the control  $Tm_G$ . The adequacy of loading in the experiments of Handley and his associates has not been explicitly referred to, and sufficient data for independent evaluation are not presented. Urine flows of less than 1 ml./min. during the measurement of  $Tm_G$  seem hardly compatible with high load/ $Tm$  ratios (26). India ink was injected in rat aortas by Still (31), and he found glomeruli not uniformly filled. The results are interpreted as indicating intermittence.

A phenomenon which has implications for the measurement of glomerular filtration as well as for other aspects of the study of renal function is that of urinary delay time. Several studies relevant to this subject have appeared. Michie & Michie (32) find that when infusion of substances is started at constant rate, equilibrium (as indicated by constancy of the clearance) is not achieved for some 20 min. The delay is attributed to time required to "wash out" the dead space. Bradley, Nickel & Leifer (33) obtained similar results with the use of inulin and by measuring the time for the specific activity of several injected radioactive substances to reach similar levels in urine and plasma. Analysis of the results is performed on the basis of the heterogeneity of the nephron population (cf. 224,) and it is concluded that, for the normal human kidney, urine from 75 per cent of the nephrons reaches the bladder in 10 min. or less, 95 per cent in 20 min., and 100 per cent in about 30 min. All of these times are greater than ordinarily allowed for delay. Liljestrand & Swedin (34) find similarly prolonged delay for equilibrium between plasma and urine following simultaneous injection of inulin and



radiophosphate in the dog. This probably accounts in part for the apparent discrepancy between specific activities of phosphate in the plasma and urine (35), but that this may not be the only explanation is indicated by the studies of Ström (36) and the further observations of Govaerts (37). It is clear from these data that earlier estimates of delay time based on appearance time or on the estimated dead space volume divided by urine flow are erroneously low. Appearance time [a study is reported (38)] represents only the fastest moving components of the urine, while the formulation based on volume assumes a moving front of the new composition, as well as uniformity throughout the nephron population. It is clear that no uniform, if any, correction for delay time can be accurate in the presence of rapidly changing plasma concentrations and that a degree of uncertainty is introduced in all measurements when there are large and rapid changes in renal function.

#### TUBULAR TRANSPORT OF ORGANIC SUBSTANCES

The transport system responsible for secretion of *p*-aminohippurate (PAH), phenolsulfonphthalein (PSP), etc., being subject to reasonably accurate evaluation *in vivo* as well as to more extended and controlled study *in vitro*, has been the subject of extensive investigation. Information as to the nature of the process is briefly reviewed by Taggart (39). Involvement of a condensation reaction between the carboxyl group of PAH and the sulfhydryl group of coenzyme A is suggested as the fundamental step in transport. The nature of the stimulatory effect of acetate is not clear. Lactate and acetate, which enhance PAH uptake by kidney slices *in vitro* and  $Tm_{PAH}$  in the dog *in vivo*, have been shown to increase  $Tm_{PAH}$  in man (40, 41). Schacter & Freinkel have studied the "self-depression" of  $Tm_{PAH}$  observed at high plasma PAH levels in the dog (42). The effect is frequently observed at load/ $Tm$  ratios over six, but is highly variable in occurrence and extent. When it occurs, it is reversible by decreasing load, and it can be reversed or prevented by the administration of acetate. The uptake of  $PSP^2$  by guinea pig kidney slices and of PAH by rabbit kidney slices is inhibited by dehydroacetic acid, dinitrophenol, and Carinamide (4'-Carboxyphenylmethane sulfonanilide) [Shideman *et al.* (43)]; when inhibition is partial it is reversible by acetate which has similar effects on inhibited PSP clearance in the dog. The data are interpreted as in accord with other work indicating the acetate effect is not produced by its enhancement of oxidative metabolism.

Shideman & Rene (44) point out a correlation between inhibition of succinoxidase and the inhibitory effects of malonate, dehydroacetate, cinchophen, and chlorguanide on PAH transport and suggest that energy derived specifically from succinate oxidation and the Krebs cycle is involved in PAH secretion. Only minimal effects on the transport of phosphate and glucose were observed. The depressed PAH uptake by kidney slices from hypophysectomized rats is restored by prior administration of growth hormone

[Farah *et al.* (45)]. The reduced  $Tm_{PAH}$  of dogs with diabetes insipidus is increased by acetate (46). Effects of other manipulations on  $Tm_{PAH}$  are reported (47, 48, 49).

Clark & Barker (50) report renal oxygen consumption in man to be unchanged (within the not inconsiderable error in the measurement) by loading with PAH and during water and osmotic diuresis. It is suggested that energy is expended in the kidney to maintain a steady state and that this permits the performance of work. Axelrod & Pitts (51) find no change in  $Tm_{PAH}$  and  $Tm_G$  in dog or man on breathing mixtures low in  $O_2$ .

Josephson *et al.* (52) studied PAH excretion and extraction in man with rapidly rising or falling plasma concentrations. They calculate a value representing the fraction of PAH presented to the tubules which escapes in the renal vein and, finding this value to be lower when plasma concentration is increasing, interpret the results as indicating storage of PAH in tubule cells. The comments on delay time above seem pertinent to these conclusions.

A method for quantitative study of PSP concentration in kidney slices is described by Rathbun & Shideman (53). Taggart (54) reports on the binding of PAH to albumin in human and dog plasma.

Beyer and associates (55) report the physiologic effects of Benemid [*p*-(dipropylsulfamyl)-benzoic acid] and its excretion. It inhibits transport of PAH, PSP, and penicillin, does not affect GFR or secretion of N-methylnicotinamide, nor inhibit transport of electrolytes or several organic substances reabsorbed by the tubules. It increases urate clearance ( $C_U$ ) in mongrel dogs, decreases it in Dalmatians. Benemid is metabolized slowly and excreted at a rate which indicates net reabsorption by the tubules.

Sirota and his associates (56, 57) have studied the effects of Benemid and of salicylate alone and together on  $C_U$  in man. Benemid has a striking inhibitory effect on the reabsorption of urate, raising  $C_U/C_{IN}$  from .07 to .33 for 24 hr. In a patient with the Fanconi syndrome  $C_U/C_{IN}$  was 0.98 and unaffected by Benemid. Interesting results are reported with salicylate: urate excretion is increased by high levels, unchanged by moderate levels (5 to 15 mg. per cent), depressed by low levels of salicylate. A combination of effects would appear to be involved: (a) an inhibitory effect of salicylate on urate transport, (b) a removal of glycine from competition with urate for transport, by conjugation of glycine and salicylate. The latter effect appears to predominate at low levels. Interference by salicylate with Benemid effect is more difficult to explain. It may represent a blocking of the Benemid from its site of action.

Foulks and associates (58) show that a large net secretory transport of thiosulfate can be induced in the dog by chronic administration of cortisone or testosterone. A reabsorptive mechanism is also operative since Carinamide reduces thiosulfate clearance below  $C_{CR}$ . Interestingly, Benemid has no effect, nor do several other inhibitors. At levels over 20 mg. per cent, thiosulfate clearance approximates GFR under most circumstances but the authors conclude that it is not to be relied upon as a measure of GFR.

Despopoulos & Kaufman (59) report that, in dogs,  $Tm_G$  is markedly and reversibly depressed by the glucoside, but not the acetate, of desoxycorticosterone. The effect is believed to be attributable to competition for some component of the transport mechanism. Renal glycosuria in ACTH<sup>2</sup>-treated premature infants is sometimes caused by a rise in GFR, sometimes by a fall in  $Tm_G$  according to the findings of Weintraub *et al.* (60). A decrease in  $Tm_G$  with aging in man, parallel to a similar fall in  $C_{IN}$ , is reported by Miller *et al.* (61). Pitesky *et al.* (62) find the use of venous blood unsatisfactory for definitive measurements of  $Tm_G$ .

Schmidt-Nielsen (63) reports clearances of urea greater than  $C_{IN}$  in kangaroo rats, especially those fed a high protein diet. It is suggested that this indicates secretion of urea by the tubules although the author expresses reservations because of limitations imposed by technique. Clearances of urea exceeding those of inulin in the laboratory rat during administration of urea and glucose are reported by Sosnowick in a preliminary abstract (64). Kempton (65) describes studies of the reabsorption of urea by the smooth dogfish (*Mustelus canis*) indicating that the amount of urea excreted per unit of glomerular filtrate is constant over a wide range of naturally occurring urea levels.

Crampton & Smyth (66) have studied the renal excretion of the stereoisomers of alanine in the cat. D-Alanine is excreted at all levels in the plasma by a mechanism said to resemble that for urea, while the natural L-isomer is actively reabsorbed with a "threshold" of about 40 mg. per cent. Grob (67) finds that histidine is excreted in man by a mechanism normally involving reabsorption of about 93 per cent of that filtered throughout the range studied; reabsorption is depressed by ACTH or cortisone.

By extrapolation of the curve relating excretion per unit of GFR to plasma hemoglobin concentration in man, McDonald *et al.* (22) estimate that on the average 17 mg. of hemoglobin are reabsorbed per 100 ml. of glomerular filtrate.

Roholt & Schmidt (68) describe the relationship between plasma concentration and clearance of pantothenate in man. Clearance at low plasma levels is low but rises to 300 to 600 ml./min, before undergoing self-depression. Secretion is depressed by Carinamide. At elevated plasma concentration, N-methyl-2-pyridone-5-carboxylamide has a clearance between that of urea and GFR according to the findings of Holman & Lous (69).

The effect of changes in urine pH on excretion of certain acids and bases has been described earlier and has been further investigated: salicylate by Dalgaard-Mikkelsen (70) and Davis & Smith (71), gentisic acid by Batterman & Sommer (72), and procaine by Terp (73). (See also ammonia excretion.) The marked increase in salicylate excretion with rise in urine pH is confirmed in rabbits (70) and dogs (71). It is suggested (70) that the theory of selective tubule permeability to the un-ionized species cannot account for the effect of pH on salicylate excretion since the urine pH is so far removed from the pK of salicylate that essentially all the salicylate is in ionized form

at all urine pH's. However, if relatively complete impermeability to the ionized form exists and if equilibrium between tubule lumen and peritubule fluid occurs, the concentration of un-ionized salicylate must approach equality within and without the tubule. Under such conditions the observed changes in excretion (including excretion, in alkaline urine, of amounts in excess of those filtered) would be predicted and no active transport of salicylate per se would be required.

A study of the clearance of barbital ( $C_B$ ) in the dog by Giotti & Maynert (74) indicates that most of the filtered barbital is reabsorbed passively,  $C_B/C_{CR}$  averaging 0.09 at all dosage levels during water diuresis, increasing with urine flow. More striking increases of  $C_B/C_{CR}$  are produced by osmotic diuresis. The  $C_B/C_{CR}$  is not affected by urine pH but urine pH is increased by large doses of barbital. The latter is attributed to selective permeability to the un-ionized compound leaving the alkaline component behind.

#### WATER DIURESIS AND ANTIDIURESIS

Reviews pertaining to this subject by Pickford (75) and by Heller (76, 77) and a summary by Van Dyke (78) have been published.

Only a small part of the work in this field has been directed toward an elucidation of the renal mechanisms for diluting and concentrating the urine. Until further clarification of these processes is obtained and their relationship to glomerular filtration and electrolyte transport more acutely defined, many interpretations of data pertaining to this problem must remain largely in the realm of speculation. The work of two groups in particular has been aimed at defining the fundamental mechanisms; unfortunately, they are in almost complete disagreement as to the interpretation of the findings. The viewpoint of one of these groups has been summarized by Smith (79) and by Wesson (80), and much of the work from that laboratory, upon which this viewpoint is based, has appeared during the period covered by this review (81 to 85). Space will not allow description of the experimental procedures and findings; careful examination of the original papers is recommended. The results are interpreted in terms of the following processes: (a) active reabsorption of Na salts in the proximal tubule with passive reabsorption of water to maintain the isosmotic state; (b) further active reabsorption of a fixed amount of Na in the distal tubule, water following passively to maintain isosmoticity in the presence of antidiuretic hormone (ADH) but not in the absence of ADH; (c) active reabsorption of a fixed quantity of water (or less if an osmotic ceiling is reached) to form a hypertonic urine in a more distal segment, possibly the collecting duct. The data presented are largely compatible with these views although other interpretations are possible. One such interpretation is offered by West *et al.* (86) in presenting data of similar nature obtained during combined osmotic and water diuresis. These workers hold that all solute reabsorption is isosmotic and occurs in the "proximal" tubule and that dilution and concentration are effected in the "distal" tubule by transport of water in the appropriate direction [Brodsky (80)]. The con-

clusion follows directly from the expressed view of proximal tubule function. The interpretation on which the latter view is based, however, is questionable. A reproducible relationship between solute excretion and urine flow, independent of the nature of the solute, is the basis of this view. The interpretation seems to depend on a concept of "reabsorbate concentration" rather than on separate transport of solute (in large part in a combined state) and water, as is more probably the case. This leads to misinterpretation of the views of Smith and his associates as requiring a change in solute reabsorption in the transition from antidiuresis to water diuresis, whereas only a change in passive water reabsorption is required. Except by personal preference, it does not appear that these data can permit one to distinguish between non-reabsorption and secretion as the basis of water diuresis, although the dependence of urine flow on filtration would tend to lend some credence to the nonreabsorption theory. Roscoe (87) presents data from patients with renal disease and an analysis which is believed to indicate secretion of water and solutes. This would require secretion by the tubules of a solution of widely varying composition, but the statistical procedure on which it is based is open to question, since it requires extrapolation to zero of a fitted line when there is no theoretical basis for fitting this particular function nor reason to believe that values of zero for the independent variable can, in fact, exist.

Reasoning from a physical analogue [Hargitay & Kuhn (88)] and finding a gradient of total solute concentration from cortex to papilla in frozen kidney sections, Wirz *et al.* (89) offer an interesting theory for the urine concentrating mechanism. However, the criticism of Smith (79) that the proposed mechanism would require transient concentration of a large fraction of the renal blood flow seems highly pertinent.

A number of papers relating to various stimuli for the release of ADH, its metabolism in the body, and excretion in the urine have appeared. The subject is largely covered in the reviews mentioned earlier (75, 76, 77) and will be omitted from consideration here.

The defect in water diuresis following ablation of the adrenals or hypophysis and restoration of diuresis by various hormone preparations has been the subject of a number of investigations. The effect of cortisone is attributed largely to a direct effect on the renal tubules (90, 91, 92) or to delayed inactivation of ADH<sup>2</sup> (93). One paper stresses the depressed GFR in Addison's disease (94). The mechanism of this abnormality and its correction is certainly not established and, until the relationship between filtration rate and electrolyte transport on one hand and water diuresis on the other is clarified, the problem may remain subject to such differences of interpretation. The studies of Ames & Van Dyke (95), revealing no ADH in the serum of adrenalectomized rats, lend little credence to the delayed inactivation hypothesis. The delay in water excretion in protein-depleted animals and the decreased inactivation of ADH by liver homogenates of such animals may or may not be related (96 to 99). The diuretic response to water but not to saline solutions is reduced in adrenalectomized rats (100). Hofmann (101) finds

the diuretic response to water depressed in hypophysectomized rats but considerably faster than that following adrenalectomy. Injection of cortisone produces a state resembling diabetes insipidus in the normal dog [Sirek & Best (102)], but, unlike the more marked polyuria produced by desoxycorticosterone (DCA), that produced by cortisone is not lost when salt intake is restricted [Davis & Howell (103)]. Pyridoxine deficiency is associated with impaired water diuresis, attributed to adrenal dysfunction [Stebbins (104)]; restoration of water diuresis by DCA,<sup>2</sup> as was found, is surprising. A role of the adrenal medulla in water diuresis is stressed by Dexter & Stoner (105); medullectomized rats have a deficient water diuresis. An indirect effect, partially through "triggering" of adrenocortical secretion, is proposed. Papper & Rosenbaum (106) attribute the decreased diuretic response to water in "compensated" hepatic cirrhosis to persistence of antidiuretic activity, but Nelson & Welt (107) find no difference between normals and patients with cirrhosis in the time to reach maximum urine flow, nor in the intensity or duration of the antidiuresis following small doses of ADH.

Barnett and associates (108) detect no limitation of the ability of premature infants to put out a dilute urine; the relatively low volume seems attributable to a low GFR. In response to ADH the urine is concentrated to only about half the maximum attained in adults. When beta-hypophamine (Pitressin) is injected in newborn rats, however, Heller (109) finds no antidiuretic response although the ADH appears in the urine. Maxwell & Breed (110) confirm that the primary effects of ADH in man are not circulatory but are exerted on the tubule.

Leaf *et al.* (111) find that in panhypopituitarism the inability to excrete a concentrated urine, characteristic of diabetes insipidus, persists. The loss of polyuria, when anterior pituitary insufficiency is superimposed on neurohypophyseal failure, is attributed to a decreased excretory solute load, implying a floor to urine dilution. Possibly related to this phenomenon is the observation of Dempster & Joekes (112) that a kidney autotransplanted to the neck of the dog puts out only about one half the normal amount of urine during water diuresis so long as the other kidney remains in its normal position, but has a normal diuresis when the abdominal kidney is removed.

Forster (113) reports that the urine flow varies without significant changes in GFR in uncomplicated water diuresis in the rabbit; the concomitant changes in urine flow and GFR frequently observed are probably attributable to stimulation of ADH secretion by the experimental conditions.

#### TRANSPORT AND EXCRETION OF SODIUM AND CHLORIDE

Because of the central role of sodium in edema formation and many clinical disturbances, a large amount of effort is expended in this field. Many interpretations are still subject to the reservations previously expressed (114) concerning attempts to analyze the contribution of changes in glomerular filtration versus changes in tubule activity to modifications of sodium excretion.

Smith's exposition of the work and views of his laboratory is pertinent to the transport of sodium as well as water (79). Berliner (115) expresses the view that sodium transport is presumably effected by ion exchange and that it cannot be considered wholly apart from the transport of the counter-ions, hydrogen, and potassium. Black (116) has reviewed the physiology and clinical aspects of depletion of sodium and potassium.

Hoshiko *et al.* (117) present a preliminary report of double perfusion of frog kidneys with  $\text{Na}^{22}$ ,  $\text{K}^{42}$  and  $\text{D}_2\text{O}$  supplied through the renal portal vein and these experiments are further discussed by Visscher (118). The experiments indicate that large numbers of particles of these species reach the urine from interstitial fluid without entering the glomerular filtrate. This cannot be considered to demonstrate tubular secretion of these substances since their entry may represent the back flux in a system whose active component is in the opposite direction [Ussing (119)]. The rather high degree of equilibration of these substances across the tubule is surprising but may be in part attributable to the unphysiologic state of the preparation. The much smaller entry into the urine of  $\text{Na}^{22}$  and  $\text{K}^{42}$  reaching the chicken kidney via the renal portal vein in the intact animal would seem to support such an interpretation [Rennick *et al.* (120, 121)].

Levy & Ankeney (122), studying Na excretion in the dog during administration of hypertonic saline solutions, find that in those experiments in which  $C_{CR}$  is stable, reabsorption of Na remains relatively constant as plasma Na concentration is raised. This favors the view that, in considering filtered Na load, the concentration of Na is more important in determining excretion rate than is GFR [Wesson (80)]. Levy & Berne (123) attribute the reduction of Na excretion largely to decreased GFR when cardiac output in the dog is acutely reduced by graded occlusion of the pulmonary artery. When the renal arterial pressure of dogs is reduced by inflation of a balloon in the aorta, Thompson & Pitts (124) find that the fall in Na excretion is proportionately greater than the fall in  $C_{CR}$ . Selkurt *et al.* (125) report that raising ureteral pressure in dogs reduces Na excretion relatively more than GFR, but that changes in the latter function are adequate to account for the results. Frieden *et al.* (126) find that dogs, previously depleted of Na by peritoneal dialysis, excrete less Na than in the normal state at similar filtered loads when hypertonic NaCl is infused. They suggest that "alterations in connective tissue metabolism may stimulate changes in renal tubular metabolism" leading to increased reabsorption of Na. The sodium retention following ligation of peripheral veins is similarly interpreted (127). Stamler *et al.* (128) consider the retention of Na following partial ligation of the thoracic portion of the inferior vena cava of dogs to be unrelated to reduced GFR or elevated renal venous pressure. The retention of Na is viewed as an "attempt to maintain blood volume in the face of threatening hypovolemia." Similar findings are reported following the production of constrictive pericarditis, constriction of superior and inferior vena cava, and constriction of the pulmonary veins [Boucek *et al.* (129, 130)]. Davis *et al.* (131) report metabolic



balance and renal function studies following the production of constrictive pericarditis in dogs. Changes in the electrolyte pattern of stools suggest altered adrenocortical activity. Jeanneret (132) describes a procedure for explantation of the bladder of the dog and chronic studies of the function of the individual kidneys. Partial ligation of the inferior vena cava between the renal veins reduced urine flow and Na excretion on the affected side with relatively little change in GFR. The effects are attributed to the effect of increased venous pressure independent of filtered load, but the opposite interpretation could be just as well supported. The same is true of the observations of Sirota & Nabatoff on a patient who had a splenorenal anastomosis for portal hypertension (133).

Chalmers, Lewis & Pawan (134) find GFR and Na excretion simultaneously reduced in man when cuffs are inflated on the thighs. Since Na excretion usually fell further while GFR rose on release of the constriction, changes other than those in GFR must be involved. Similar results and conclusions are reported by Levitt *et al.* (135). Holland (136) was unable to reproduce the effects of head-up tilting on sodium excretion with beta-hypophamine, cortisone, ACTH, or desoxycorticosterone glucoside. Mannitol diuresis causes less sodium loss during quiet standing than in recumbency [Goodyer & Seldin (137)].

Friedman *et al.* (138) report no evidence of adrenal participation in the acute reduction of Na excretion when the inferior vena cava of rats is obstructed at various levels. In patients with Addison's disease maintained on DCA and cortisone, Rosenbaum *et al.* (139) find a normal diurnal rhythm of fluid and electrolyte excretion and a normal response in electrolyte excretion to change in dietary Na intake, change in posture, venous congestion and administration of hypotonic saline solution. Petersdorf & Welt (140) report that injection of concentrated albumin solutions decreases excretion of Na and  $H_2O$  without decreasing endogenous  $C_{CR}$ .

The effect of intravenous digoxin on Na excretion in congestive heart failure seems to be attributed largely to changes in GFR by Davison & Gaddie (141), but Eichna *et al.* (142) consider the relationship to renal venous pressure more consistent. In cirrhotics who stop accumulating ascites, Leslie *et al.* believe a rise in  $C_{IN}$  may be an important factor (143).

The hypothesis that Na excretion in man is controlled through a "volume receptor" responsive to changes in extracellular fluid (ECF) volume in the cranial cavity has received further study. Compression of the neck increased Na excretion in the sitting but not the recumbent position; changes in endogenous  $C_{CR}$  were inconsistent [Viar *et al.* (144)]. Compression of the legs in the sitting position increased Na excretion [Lusk *et al.* (145)]. But compression of the neck did not increase Na excretion in subjects with congestive heart failure [Lombardo & Harrison (146)]. The mechanism by which these changes in Na excretion are produced when they do occur is not clear; it seems not unlikely that inflation of a blood pressure cuff around the neck has effects in addition to elevation of intracranial venous pressure. "Volume

receptors," not specifically localized, are considered to be involved in the changes in Na excretion when an arteriovenous fistula is closed [Epstein, Post & McDowell (147)] and in the increased excretion of Na which follows expansion of the ECF<sup>2</sup> with hypotonic saline [Strauss *et al.* (148)].

Goodyer & Glenn (149) have examined the mechanism of osmotic diuresis by injections directly into the renal artery in dogs. The injection of mannitol, urea, and hypertonic solutions of Na salts greatly increased the excretion of Na and water on the injected as compared to the opposite side. Twenty-five per cent albumin solutions had an inconstant depressing effect on these functions. These findings would appear to exclude changes in water distribution, in the body as a whole, as primarily responsible for this type of diuresis. The authors attribute the loss of Na largely to an increase in velocity of flow rather than to the development of a concentration gradient from tubule to interstitial fluid because such a gradient would not develop when hypertonic sodium salts are injected. However, it is not certain, or even probable, that the mechanism (of electrolyte loss) is the same when nonelectrolytes and sodium salts are injected. Tarail *et al.* (150) produced diuresis with hypertonic glucose solutions in edematous patients and find less sodium excreted than in normal subjects under the same conditions. The data indicate, as have earlier studies, that the sodium loss during osmotic diuresis is not independent of other influences, but modification of the generally held views as to mechanism would not seem indicated. Assali *et al.* (151), on the other hand, find no abnormality of excretion of Na and Cl during mannitol diuresis in patients with toxemia of pregnancy even in the presence of edema; concentrating capacity was impaired. Brodsky *et al.* (152) propose the use of osmotic diuresis for the evaluation of capacity for water and electrolyte conservation.

Denton and associates have studied electrolyte losses through duodenal fistulae in man and esophageal fistulae in sheep (153, 154) and the nature of the renal compensation. This is interpreted in terms of the distortion of the Na/Cl ratio.

In a mixed group of cardiacs, hypertensives, and normal individuals, Green *et al.* (155) find a significant correlation between Na excretion and arterial blood pressure. It is difficult to believe that other factors are not involved.

Nickel *et al.* (156) have examined renal function and electrolyte excretion in patients with chronic renal insufficiency. When salt intake is restricted, the fall in Na excretion is associated with a decrease in  $C_{IN}$ . The fractions of filtered Na, Cl, and water excreted in the urine exceed the highest values attained in salt-loaded normal individuals.

*Effects of hormones on sodium excretion.*—Roberts & Pitts (157) report that intravenous injection of cortisone in acute experiments in adrenalectomized dogs leads to a marked decrease in sodium excretion. Prolonged daily administration restores lowered GFR toward normal and corrects the abnormal levels of sodium and potassium in the plasma. The effects are con-

sidered similar to and additive with those of DCA. On the other hand, in chronic studies on normal dogs, Davis & Howell (103) find that cortisone induces an initial loss of sodium presumably because of a marked increase in GFR with only a weak effect toward increased Na transport by the tubules. In adrenalectomized dogs Swingle *et al.* (158) observe that cortisone maintains the animals in good health but does not prevent a fall in plasma Na and a rise in plasma K concentration.

Alexander *et al.* (159) administered large doses of ACTH to patients; decreased Na excretion resulted from increased Na transport by the tubules, despite an increase in GFR. The latter probably contributed to the secondary increase in Na excretion after 10 to 14 days. Ingbar and associates (160) report depression of urate and phosphate transport with ACTH, and find that excreted PAH was covered by more K relative to Na than in control observation. Forsyth (161) reports an increase in excretion of Na by mice under NaCl load when DCA is administered in small doses; the effect is attributed to decreased Na transport but GFR was not measured.

Simpson & Tait (162) and Marcus *et al.* (162a) describe bioassay methods, using adrenalectomized rats, for effects on electrolyte excretion obtained with a number of substances of adrenal origin. Chart and associates find a sodium-retaining factor in the urine of patients with toxemia of pregnancy (163) and edema (164). Groen *et al.* (165) report that glycyrrhizinic acid (licorice extract) can replace DCA in the maintenance of patients with Addison's disease. Green & Williams (166) find, in confirmation of earlier reports, that butazolidine causes retention of Na and Cl. Whether this is a direct effect on transport, an effect mediated by the adrenals, or a hemodynamic effect has not yet been established.

Rolf, Surtshin & White (167) find that hypophysectomized dogs on rigidly restricted Na intake show a greater fall in plasma Na concentration than do normals, but the evidence that this is a result of negative Na balance is not convincing. Lane & de Bodo (168) report no pituitary tissue on serial section in dogs previously reported (169) to be able to conserve Na on prolonged restriction and to excrete K under load. These findings suggest that, in the dog, hypophyseal adrenocorticotrophic effects may play little role in regulating Na excretion. Martin & White (170) find that hypophysectomized dogs excrete a salt load at the same rate as the normal, while normal dogs given 1 mg./day of DCA excrete such a load faster than adrenalectomized dogs on the same regimen. Stein *et al.* (171) produced a transitory retention of Na and Cl, and a continuing retention of K and nitrogen by administering growth hormone to adrenalectomized rats.

Sawyer (172) finds that the excretion of Na, K, and Cl in rats is increased by what are sometimes referred to as "pharmacologic doses" of beta-hypophamine (Pitressin) (100  $\mu$ u/kg.); the basis for such a designation is not unquestionable. On the other hand, Holland & Stead (173) produced no change in Na excretion in man when antidiuresis was maintained for 24 hr. A similar lack of effect in man is reported by Black & Thomson (174).

Kaplan *et al.* (175) have examined the effects of epinephrine and L-norepinephrine on Na and Cl excretion during mannitol diuresis in dogs. The reduction in electrolyte excretion after epinephrine is attributed to a direct effect on transport by the tubules. L-Norepinephrine, in the dosage used, produced only slight and inconstant alterations in urinary excretion. Smythe *et al.* (176) reach similar conclusions as to the effects of epinephrine in man but these workers have obtained the same renal effects with norepinephrine as they did with epinephrine. Prolonged administration of epinephrine in oil to man increased excretion of Na and Cl and decreased excretion of K [Duncan *et al.* (177)]; no evidence was found to suggest stimulation of adrenocortical activity. In hydrated rats, norepinephrine had no effect on electrolyte excretion [Eversole *et al.* (178)]. In saline-loaded animals they find the most striking effect of norepinephrine to be an increase in urine flow; epinephrine was antidiuretic. It is not clear whether these conflicting findings with adrenal medullary hormones represent species differences or the effects of varying experimental conditions.

*Effects of the renal nerves.*—Whether the renal nerves exert a modifying influence on tubular transport or whether observed differences between normal and denervated kidneys are the result of circulatory changes is a highly controversial question and opinion is about evenly divided. The difference is almost entirely one of opinion since there is substantial agreement on the experimental findings. The problem devolves upon the effect of relatively small changes in GFR on Na excretion when other conditions are more or less constant, as is probably the case in this instance, where the denervated kidney is compared with the normal. Kaplan *et al.* (179) find a considerably greater excretion of Na and Cl from the denervated kidney during mannitol diuresis, with the GFR quite appreciably higher than that of the normal kidney. They attribute the difference to a deficit of Na reabsorption as the result of a change in the tubular activity in the denervated kidney. Blake (180) and Sartorius & Burlington (181) are in general agreement. Surtshin *et al.* (182) find no difference in hemodynamic function or electrolyte excretion between normal and denervated kidneys in the unanesthetized dog. When anesthesia is induced or following some painful stimuli,  $C_{PAH}$ ,  $C_{IN}$ , and electrolyte excretion fall on the normal but not the denervated side with the drop in electrolyte excretion relatively greater than in the  $C_{IN}$ . They attribute the changes entirely to the change in GRF. Berne (183) reports almost identical experiments and conclusions. Surtshin & Hoeltzenbein (184) find that the denervated kidney has an increased vasomotor response to the action of epinephrine. Berne *et al.* (185) are in agreement, but find, in addition, changes in Na excretion in both kidneys which did not seem to be related to changes in GFR and are attributed to a specific effect on sodium transport.

*Effects of diuretics.*—A number of studies have utilized mercurial diuretics (Hg) with the purpose not only of examining their mode and site of action but with the hope of throwing light on some of the mechanisms involved in

electrolyte transport. Although there are but few points of disagreement as to the effects produced, there are considerable differences in interpretations. A major cause of the latter arises from varying views of the function of various segments of the mammalian tubule; since information on this subject is so limited, there is ample room for speculation and widely varying opinion.

Much work has dealt with the effects of mercurial diuresis on total urinary solute concentration. Brodsky & Graubarth (186) studied the solute concentration after administration of Hg to hydropenic dogs. The same relationship between urine flow and total solute excretion was observed as is obtained with osmotic diuresis. Since, in their opinion, all solute reabsorption occurs in the "proximal" tubule, they locate the site of action of Hg there. Weston *et al.* (187) and Welt *et al.* (188) believe that Hg exerts its effect on the "proximal" tubule in man because during the action of beta-hypophamine the increment of fluid and electrolyte excreted constitute a solution essentially isotonic with ECF. However, an effect of Hg during ADH action on a distal tubule, the function of which corresponds to the views of Smith and his associates (79), would also yield these changes. Farah, Cobbey & Mook (189) studied the concentration of only Na and Cl in the urine of dogs before and after the administration of Hg. Because of changes in these concentrations they conclude that the effect cannot be on any one segment of the tubule, but the data, since they do not include total solute concentration, are not conclusive. Capps *et al.* (190) find no effect of Hg on the capacity of either man or dog to form a hypertonic urine. In experiments done under water diuresis, the increase in electrolyte excretion was usually not accompanied by an increase in urine flow. Such a finding would be compatible with an effect on the distal tubule as the latter is defined by Smith (79) and corresponds to the observations of Ladd (81) on the effect of mercaptomerin (Thiomerin) in man. Ladd interprets his data to indicate that Hg blocks a part of distal tubular transport of Na. In the dog, however, Wesson & Anslow (82) find that when Hg is given during water diuresis urine flow does increase in proportion to the increased electrolyte excretion and localize the effect of the proximal tubule as they define it. These investigators agree with Farah *et al.* (191) and Mudge *et al.* (192) that the increment of Na excretion after Hg may exceed 20 per cent of the control reabsorption and, if one accepts that only 15 to 20 per cent of the reabsorbed Na can be reabsorbed by the distal segment, the action of Hg cannot be confined to the distal tubule. Weston *et al.* (193) have attempted to localize the site of action of Hg in man by looking for inhibition of other transport processes. They find no effect on ammonia excretion, an increase in titratable acid, and conclude that "much of the diuretic action of Hg is exerted on the proximal tubule." It would seem a likely possibility that Hg might inhibit one transport system in one segment, another in a different part of the tubule. However, there is, at present, no evidence that acidification and ammonia excretion are functions of the distal tubule in the mammal. Rice

*et al.* (194) show that previously salt-depleted dogs, infused with 1.5 per cent NaCl solutions and given meralluride sodium (Mercurhydrin), excrete less Na than they do when not salt-depleted. They conclude that if facultative Na reabsorption is confined to the distal tubule, Hg must act in the proximal segment. There is no evidence that facultative Na reabsorption is confined to the distal tubule.

The mechanism by which acidifying salts potentiate the action of Hg constitutes a problem of considerable interest. Axelrod & Pitts (195) find no enhancement with respiratory acidosis, no inhibition of the diuresis when the urine was rendered alkaline by administration of a carbonic anhydrase inhibitor. In their acute experiments in dogs diuretic response was directly related to plasma Cl concentration; they suspect that it is Cl transport that is inhibited, that the potentiation is a result of elevation of the plasma chloride. Hilton (196), on the other hand, finds that potentiation continues, in patients placed on ammonium chloride, after increased ammonia formation has permitted return of the plasma anion pattern to control levels. Although the mechanism is by no means clear, elevation of the plasma chloride does not appear to be necessary.

Axelrod & Pitts (198) show that anoxia suppresses Hg diuresis in dogs even if respiratory alkalosis is prevented by inhalation of 5 per cent carbon dioxide. They find the suppression can be produced by ACTH. Weston *et al.* (199) report similar suppression with DCA in man. On the other hand, Farah (200) finds no decrease in the effect of Hg when dogs are pretreated with DCA, desoxycorticosterone glucoside, or ACTH.

Schwartz & Wallace (201), Hilton (202), and Lesser *et al.* (203) have studied electrolyte losses during Hg diuresis in edematous patients. All find chloride losses tending to exceed that of Na and stress the considerable losses of potassium.

Weston *et al.* (204) and Grossman *et al.* (205) have examined the distribution, and the urinary and fecal excretion of mercury after the intravenous administration of mercurial diuretics. Short (206) has investigated the effect on diuretic potency and toxicity of combination of mercurials with 2,3-dimercaptopropanol (BAL).

Dicker (207) reports the effects of various diuretics on newborn rats and puppies. Kattus *et al.* (208) find a derivative of 6-aminouracil to be an effective diuretic when administered by mouth to edematous patients. Little (80, 209) detects a diuretic substance in concentrates of human and pregnant mare urine and describes a procedure for assay of diuretic substances.

Sellers and associates (210) find that renin increases excretion of Na, Cl, and water in the rat while decreasing  $C_{CR}$ . A marked increase in water turnover, enhanced by addition of NaCl to drinking water, is described in rats given renin intraperitoneally but not subcutaneously [Croxatto *et al.* (211)].

Stamler (212) detects no effect on transport of Na and K from a number of organic substances transported by the tubules. Pines & Perera (213)

report significant negative Na balances in subjects given sodium thiocyanate and suggest the effects may be produced by cyanide formed from the thiocyanate.

#### SECRETION OF POTASSIUM, HYDROGEN, AND AMMONIUM IONS

It has been proposed that K and H ions are transported by a mechanism which, at least in part, they share in common [Berliner, Kennedy & Orloff (214)]. Inhibition of urinary acidification by the powerful carbonic anhydrase inhibitor 6063<sup>2</sup> (diamox) was found to result in a marked increase in the excretion of K; the increase was shown to be inhibited by mercurial diuretics and is considered to result from enhanced tubular secretion of K. This observation, taken with a number of others indicating a relationship between urine acidification and K metabolism, is considered to suggest that K and H ions compete for some component of a mechanism by which both are exchanged for Na. Essentially similar experimental findings are reported from administration of 6063 to normal and cardiac patients by Friedberg *et al.* (215). The basis of the competition hypothesis and its implications are discussed further by Berliner (115). It is pointed out that, when 6063 is administered, between 40 and 50 per cent of the filtered bicarbonate may be excreted even in the presence of severe acidosis. This could not result from inhibition of H ion secretion if the secretion were limited to the distal tubule, as the latter is usually conceived; it is proposed that all bicarbonate reabsorption is accomplished by H-Na exchange. The reabsorption of bicarbonate in dog, man, and sheep is increased when carbon dioxide tension ( $p\text{CO}_2$ ) is elevated by inhalation of gas mixtures of high  $\text{CO}_2$  content [Brazeau & Gilman (216); Dorman & Sullivan (217); Elkinton *et al.* (218); Denton *et al.* (219)]. The effect is related to the  $p\text{CO}_2$ , not to plasma pH (216, 217); it cannot be determined whether elevation of cellular  $p\text{CO}_2$  or the resultant depression of cell pH is directly responsible, but the reviewer leans to the latter view. The observations appear to explain the changes in plasma bicarbonate in respiratory acidosis and alkalosis. They are interpreted (216, 217) as in accord with the view (115) that all bicarbonate reabsorption is effected by exchange of H for Na. Depression of K excretion in man (218) and in the sheep (219) as H secretion increases in respiratory acidosis is in accord with the competition hypothesis.

Respiratory alkalosis produced by hyperventilation has been studied in man by Singer *et al.* (220) and Stanbury & Thomson (221) and in the dog by Brazeau & Gilman (216). A rise in the excretion of Na, bicarbonate, and K indicate that the effects are the converse of those when  $p\text{CO}_2$  is elevated, and similar interpretations are warranted.

Goodyer *et al.* (222) find that osmotic diuresis with glucose reduces bicarbonate excretion in man presumably by lowering the concentration of bicarbonate in the ECF. Pitts (223) presents a general summary of acid-base regulation.



The significance of  $p\text{CO}_2$  in urine has been reinvestigated in the dog by Kennedy *et al.* (224). They find that in each pH range the  $p\text{CO}_2$  is directly related to the urinary concentration of buffer other than bicarbonate. They consider this not in accord with the hypothesis that elevation of  $p\text{CO}_2$  in urines of high pH is the result of addition of H ions in the distal tubule. The  $p\text{CO}_2$  can be explained by mixing of urines of varying pH and buffer content, issuing from heterogeneous nephrons, in a region unfavorable to back diffusion of  $\text{CO}_2$ .

Detailed studies of renal function in a patient with Fanconi syndrome are reported by Milne *et al.* (225). Pines & Mudge (226) describe studies in several patients with renal tubular acidosis. The finding of retention of K (as well as Na, water, and phosphate) when Na bicarbonate is administered is of interest and difficult to explain; it may represent suppression of K-Na exchange when the stimulus for Na retention is reduced by repletion of the extracellular Na.

That K is filtered in quantities more than adequate to account for normal K excretion is apparent. In confirmation, Bott (227) finds the concentration of K in glomerular fluid of *Necturus* the same as that in simultaneously obtained plasma. It is by no means certain, however, that filtered K contributes significantly to the K actually excreted. As a working hypothesis, to which none of the data available to date are contrary, it is convenient to assume that all of the filtered K is reabsorbed and the excretion of K is entirely dependent on the secretory process. That K reabsorption can be complete enough to accord with this view (as well as secretion negligible under some conditions) is indicated by the study of Fourman (228) which confirms earlier observations indicating that in normal subjects depleted of K, excretion of K may fall to very low levels. It is proposed that urinary loss of K, such as has been observed in K-depleted patients with severe illness, may be attributable to adrenocortical activity.

Potassium secretion, demonstrated by excretion of amounts in excess of those filtered, was found to contribute to the loss of K in a patient with an unusual potassium-losing defect [Earle *et al.* (229)]. Defective reabsorption was considered to be a factor, but this interpretation is one of personal preference which cannot be established with certainty. Excretion of more K than can be accounted for by filtration is a frequent finding in patients with marked renal insufficiency (156, 230). The most likely explanation would seem to be unmasking of a continuously operating process when the amount filtered is greatly reduced by loss of filtering capacity. The sheep is added to the species in which K secretion has been demonstrated [Denton *et al.* (154)]. Pullman & McClure (231) studied changes in K excretion in subjects given L-norepinephrine and find a reduction in K excretion highly correlated with changes in  $C_{\text{PAH}}$ , but not with GFR and Na-excretion which appear to have increased in these studies. With the tentative assumption that reabsorption should vary with the amount filtered and secretion with the amount delivered to the tubules, they suggest that changes are mediated by K secretion.

Roberts *et al.* (232) have examined the effects, in the dog, of infusions of KCl and administration of 6063<sup>2</sup> on K excretion, acidification of the urine, and acid-base balance of the ECF. The depression of acidification and the increase in K excretion described by earlier work is confirmed. The fall in ECF bicarbonate is found to be too great to be accounted for by loss of bicarbonate in the urine, and it is suggested that  $\text{KHCO}_3$  enters cells. The changes in renal excretion are interpreted in terms of bicarbonate reabsorption (as opposed to H ion secretion), but the data are not discordant with more recent views which would place the changes in ion exchange rather than strictly reabsorptive processes. The effects are roughly correlated with the plasma K level, but this may be fortuitously related to the conditions of the experiments since other studies strongly suggest that it is intracellular composition which is governing in regard to these processes.

Foulks, Mudge & Gilman (233) report the effect of infusing lithium (Li) chloride on electrolyte excretion in the dog. Approximately 30 per cent of the filtered Li is excreted in the urine despite changes over a wide range in plasma Li concentration, and the fraction excreted is not affected by mercurial diuretics or loading with K salts. The reabsorptive process is considered to be one of backdiffusion. There is a striking increase in K excretion when Li is infused and the increase is presumably in secretion since it is inhibited by mercurial diuretics. This is apparently not mediated by inhibition of carbonic anhydrase since Li had no effect on the activity of this enzyme *in vitro*. However, Orloff & Kennedy (234), examining the phenomenon further, find that the effect on K secretion is accompanied by, and presumably related to, an inhibition of urine acidification.

In considering the implications of the hypothesis of K-H ion competition, Berliner *et al.* (214) suggest that the alkalosis frequently associated with K-depletion might have its basis in a net loss of acid from the body as a result of excessive H ion secretion in the presence of a decreased K concentration. It is apparent from other studies which have appeared later that additional factors are involved. Cooke *et al.* (235) produced K depletion and alkalosis in rats by a high Na, low K intake and injection of DCA. When this regimen was interrupted and KCl administered, the alkalosis disappeared but the urine excreted was more acid and contained more ammonia. They suggest that the alkalosis is extracellular and that the intracellular fluid is actually more acid than normal in K-deficiency alkalosis. Although diet, the source of the residues which require the excretion of acid and ammonia, was not controlled in these experiments, the essentials of the conclusions are supported by a number of observations. Black & Milne (236) produced K depletion by dietary restriction in normal men and found the urine became more alkaline while alkalosis was developing and interpret their data to indicate a shift of H ions into cells. Gardner *et al.* (237) find the carbon dioxide content of muscle from K-depleted rats to be low, suggesting intracellular acidosis. Orloff *et al.* (238) administered K salts to nephrectomized, hypo-

kalemic, alkalotic rats and found that the extracellular alkalosis was relieved although there could be no loss to the external environment. The apparent shift of bicarbonate into cells when KCl is infused in the normal dog [Roberts *et al.* (232)] is apparently a similar phenomenon and not distinguishable, in effect, from exchange of K for H across the cell membrane. It would thus appear that the excess of bicarbonate in the ECF in hypokalemic alkalosis can be accounted for by internal shifts. The role of the kidney would appear to be dual: as the channel through which K loss initiates the disorder in most instances, and as the organ whose behavior maintains the elevated bicarbonate concentration. The latter requires increased secretion of H ions by the tubules relative to the normal.

Darrow *et al.* (239) from analyses of kidneys from rats with hypokalemic alkalosis could detect no definite evidence of change in the intracellular composition of kidney; but the partition of kidney electrolytes into intra- and extracellular fractions is notoriously uncertain, and it is difficult to believe that changes do not actually occur. Cooke *et al.* (240) have analyzed muscle from rats with respiratory acidosis and find minimal changes in electrolyte composition with K at the upper limits of normal and Na slightly depressed. Cooke & Segar (241) propose a mechanism for regulation of muscle composition dependent upon extracellular concentration of K and H ions; this would require that extracellular K concentration be closely regulated by renal function whereas most observations indicate that K excretion is very poorly related to its concentration in the plasma.

The lowered concentration of Cl in the plasma in hypokalemic alkalosis is often attributed to loss of Cl from the body, and explanations for such losses have been sought. However, Schwartz, Cohen & Wallace (242) find the total body Cl normal in rats with hypokalemic alkalosis and, although the changes in the subjects studied by Black & Milne (236) were small, Cl balance was positive as hypochloremic alkalosis developed. The low plasma Cl can be accounted for by dilution with bicarbonate containing fluid.

Schwartz & Relman (243) describe the findings in two patients with marked K depletion as a result of overuse of laxatives. There was marked impairment of capacity to concentrate the urine and depression of  $C_{IN}$ ,  $C_{PAH}$  and  $T_{mPAH}$ . There was a dissociation of ammonia excretion from urine pH (24 hr. collections). The authors stress the indifference of urine pH and titratable acidity to large changes in K excretion, but there was a striking reciprocal relationship between net acid excretion (mainly ammonia) and K excretion as repletion of K was effected. Alkalosis was minimal in one patient, absent in the other. In this connection the studies of Fourman & Ainley-Walker (244) are pertinent. In subjects depleted of K by the administration of large doses of ion exchange resin in the hydrogen and ammonium cycle, a moderately severe acidosis was produced. Such observations indicate that a very acid intake may more than over-balance the tendency to the development of alkalosis, and it is perhaps worth noting that there

was a rise of plasma bicarbonate to 6 to 7 m.eq./l. above control levels in the period between the stopping of resin intake and the establishment of K repletion.

Sartorius, Calhoun & Pitts (245) find a limited capacity of adrenalectomized rats to excrete titratable acid and ammonia under stress. Roberts & Pitts (246), however, find no increase in excretion of K or titratable acid in dogs given cortisone or DCA and infused with phosphate, and adrenalectomized animals maintained on NaCl behave similarly. Fourman *et al.* (247) find the effect of DCA to differ from those of ACTH and compound F; with the latter increased excretion of K predominates from the onset of the effect, while DCA causes a predominant Na retention. The significance of this observation in terms of renal mechanisms is not clear.

Seldin, Welt & Cort (248) find that there is no loss of K nor alkalosis when DCA, cortisone, or ACTH are administered to patients or rats maintained on a very low Na intake. Similar observations are reported by Relman & Schwartz (249). These findings are in accord with the hypothesis that K is excreted by exchange for Na, that this process is enhanced by adrenocortical hormones but dependent upon the load of sodium reaching the mechanism; the latter is most closely related to total electrolyte excretion.

Schlegel (250) reports a rise in the pH of rabbit urine following injection of epinephrine, norepinephrine, and hemoglobin.

The excretion of ammonia, other factors being equal, appears to be a function of urine pH despite dissociation in some circumstances. The hypothesis of Pitts (251) that ammonia enters the urine by diffusion in the uncharged state and becomes ammonium ions by combination with H ions seems most in accord with the mass of observations. Confirmation is indicated in the studies of Ferguson (252) which showed that excretion of ammonia followed urine pH whether changes in the latter resulted from administration of  $\text{NaHCO}_3$  or a carbonic anhydrase inhibitor; excretion was thus dissociated from plasma acid-base composition. A similar relationship between urine pH and  $\text{NH}_3$  excretion was noted in the studies of Stanbury & Thomson (221). Exceptions to this relationship are frequently noted. The increase in excretion when amino acid precursors of ammonia or glutamine are administered [Kamin & Handler (253)] is one, the basis of which is obvious. Another is the increased ammonia excretion which occurs over a period of several days when acidifying salts are administered. Davies & Yudkin (254) demonstrate that this phenomenon, in the rat, is accompanied by an increase in the production of ammonia by kidney slices *in vitro*. The stimulus to this increased ammonia formation is not clear since it continues after the acidosis has disappeared as a result of the compensation.

Other exceptions to the usual dependence of ammonia excretion on pH are noted and not easily explained. In the patient with the Fanconi syndrome studied by Milne *et al.* (225) ammonia excretion was high relative to urinary pH. De Oliveira (255) reports normal ammonia excretion with alkaline urines

in four patients recovering from tubular necrosis. Schwartz & Relman (243) note dissociation of pH and ammonia excretion in their K-depleted patients and when DCA was administered to normal subjects (249). The latter are based on 24 hr. urines, and it is not certain that the relationship between ammonia and pH was absent when the urine was formed.

The deficiency of ammonia excretion in adrenal insufficiency noted by earlier workers and confirmed in rats by Sartorius *et al.* (245) has been studied in the dog by Harris *et al.* (256). They find a deficient response to acidosis in the insufficient dog, but not in the adrenalectomized dog maintained on DCA or salt. Salt depleted normal dogs had a normal response. Hypophysectomized dogs excreted normal amounts of ammonia according to Hartmann *et al.* (257). White & Rolf (258) studied renal glutaminase activity and found it normal in the rat with adrenal insufficiency. Rabbits, known to excrete very little ammonia, had less than one tenth the renal glutaminase activity of rats and dogs.

#### RENAL CIRCULATION AND HEMODYNAMICS

Gomez (259) presents equations for calculation of the various renal resistances, based on measurements of mean blood pressure (BP), renal blood flow (RBF), renal plasma flow (RPF), GFR, serum protein, and renal venous pressure.

Swann and his associates report several studies of interstitial pressure (IP) and its significance. They find IP<sup>2</sup> to average 25 mm. Hg and to vary directly with arterial BP<sup>2</sup> (260), to be elevated when dogs are rendered hypertensive by perinephritis but not by arterial constriction (261); IP was unchanged in dogs with chronic congestive failure as a result of pericarditis with effusion (262). Pressures measured in arcuate veins are close to the IP and vary with it; a sharp drop in pressure is observed as the catheter tip through which it is measured is drawn into the interlobar veins (39, 263). Gottschalk (264), using a different technique, finds the average IP somewhat lower (16 mm. Hg) in dogs, still lower in rodents and cats. Winton (265, 266) reviews earlier and more recent studies of various renal hydrostatic pressures, and presents a preliminary report of interstitial pressures in dogs which appear to be similar to those of Gottschalk.

Shipley & Study (267) report on measurement of RBF,<sup>3</sup> GFR, and extraction of inulin as arterial pressure was varied over a wide range in the dog kidney perfused *in situ*. RBF, GFR, and inulin extraction rise rapidly between arterial pressures of 20 and 80 mm. Hg., then remain relatively constant up to 180 mm. Hg. RBF then rises rapidly, with GFR constant. Urine flow reached 25 to 75 per cent of GFR at pressures over 250 mm. Hg. De Wardener & Miles (268) find that RBF remains constant in the kidney perfused at pressures between 80 and 220 mm. Hg. This autoregulation is lost after renal vasoconstriction is induced by hemorrhage, and RBF is then directly related to perfusion pressure.

Ritter (269) finds no effect of arterial pulse pressure on RBF in the dog, and Goodyer & Glenn (270) find  $C_{IN}$ ,  $C_{PAH}$  and excretion of water and electrolytes unaffected by elimination of the pulse pressure.

Share (271) finds RPF increased, GFR not appreciably affected when blood viscosity of dogs is reduced by replacing large volumes of blood with plasma. Constriction of afferent arterioles is deduced. Blegen *et al.* (272) report similar findings in man. Marshall *et al.* (273) induced polycythemia in dogs by intermittent exposure to simulated altitude and find RPF slightly increased but RBF approximately doubled; GFR and filtration fraction were also increased.

Smith *et al.* (274) find that exercise, a hot environment, and dehydration all decrease mannitol clearance in man, and the effects are additive. Blake (275) reports minimal effects on renal function in dogs from moderate exercise, but emotional stress decreased sodium excretion without changing  $CCR$ .

Kopecky *et al.* (276) have noted anuria in apneic dogs maintained by diffusion respiration. This is markedly delayed by denervation of the kidney.

Changes in renal function with age are apparently attributable primarily, but not entirely, to vascular changes, and response to vasodilators is normal [Shock (277) and Landowne & Shock (278)]. Renal extraction of PAH does not change with age [Miller *et al.* (279)].

Werko *et al.* (280) studied renal hemodynamic function in patients with mitral valvular disease and find  $C_{PAH}$  low,  $C_{IN}$  low to normal, and a fair correlation between  $C_{PAH}$  and pulmonary arterial pressure. The lowering of renal blood flow when cardiac output is reduced in dogs is not mediated by the renal nerves since the response is the same in the normal and the denervated kidney [Berne & Levy (281)].

*Effect of drugs on the renal circulation.*—A number of studies have dealt with the effect of drugs on renal function. Space will not permit analysis of the results, and they are catalogued here for reference. The effect of hexamethonium in man has been reported by Kirkendall & Culbertson (282), Haugen & Blegen (283), McQueen (284), Evans & Enderby (285), and Moyer & Mills (286), and in the dog by Moyer *et al.* (287). Renal circulatory responses to pentamethonium in man are described by Miles *et al.* (288) and by Mackinnon (289). Results obtained with L-hydrazinophthalazine in man are presented by Mackinnon (289) and by Wilkinson *et al.* (290) and in the anesthetized dog by Moyer, Handley & Huggins (291). The effects of magnesium sulfate in children are reported by Etteldorf *et al.* (292), those in the dog by Harris & De Maria (293). Brandfonbrener & Geller note the effects of N-(2-chloroethyl)dibenzylamine (Dibenamine) in shocked dogs (294). Crosley *et al.* (295) report the effects of phenylephrine in man. The action of quinine in the dog is described by De Jongh *et al.* (296). Meilman (297) reports observations on veratrum in man. The effects of diphenethylcarbinamine were observed by Knoefel *et al.* (298). Glauser & Selkurt (299)

describe the effects of barbiturates on renal function in the dog. Miller & MacDonald (300) find that intravenous injection of hemoglobin causes renal vasoconstriction in man.

The responses of the renal circulation to epinephrine and norepinephrine in various species are described by Barrie *et al.* (301), Churchill-Davidson *et al.* (302), Jacobson *et al.* (303), Houck (304), and Moses (305).

The effects of plasma volume expanders are reported upon as follows: dextran by Fleming *et al.* (306), and Michie & Ragni (307); gelatin by Michie *et al.* (308, 309). The results with large volumes of isotonic saline solution are given by Crawford & Gaudino (310).

*Renal Injury.*—Oliver, MacDowell & Tracy (311) present detailed studies on the pathological anatomy of kidneys following acute renal failure. Two types of tubule injury are described: (a) nephrotoxic necrosis involving the proximal tubule of all nephrons and (b) disruption of the tubules, as a result of focal ischemia, which may involve any segment and distributed at random through the nephron population. The lesions appear in varying proportions depending on the nature of the renal insult. Roof *et al.* (312) describe the recovery of function in dog kidneys subjected to two hours of artery occlusion; persistent loss of function corresponded roughly to the substance lost in multiple infarctions.

Block, Wakim & Mann (313, 314) report studies on renal circulation and function during prolonged stimulation of the renal nerves in the dog. Both blood flow and function fall precipitously at first and then return to nearly normal values as stimulation is continued for one to two hours. Constriction was limited to the cortical area although flow ceased for a short period; blood was static in the medullary region and shunting was not observed. Block *et al.* (315) describe the effect of prolonged hypotension produced by use of a bleeding bottle. Hypotension longer than six hours in duration frequently led to severe anatomical damage, but death in renal failure was unusual. The medullary region was congested but not because of increased flow. Block *et al.* (316, 317, 318) report further observations indicating that shunts do not play a functional role in the kidney. Franklin *et al.* (319) find that intense anoxia and hypercapnia decrease cortical blood flow in the rabbit kidney, a response simulated by stimulation of the renal nerves and abolished by renal denervation but not by thoracic cord transection. Franklin (320) also describes blanching of the innervated renal cortex upon distention of the uterus. Moses & Schlegel (321) find small regions in the juxta-medullary area of the rabbit kidney preserved after ligation of the main renal artery by anastamotic circulation from the capsule and hilar region. Scher (322) measured focal blood flow in the dog kidney with heated thermocouples and finds simultaneous and parallel changes in cortex and medulla; the results are interpreted as evidence against the occurrence of shunting. Rothlin & Cerletti (323) find no evidence of A-V anastomoses by the injection of glass beads in the renal artery of anesthetized rabbits. The concept of



shunts which draw blood off from the renal cortex by permitting it to pass freely through the medulla would now appear to be a thoroughly "dead horse" in need of decent burial.

#### MISCELLANEOUS

A group of papers which do not seem to fit into any of the categories into which this review is divided are summarized here.

McCance & Widdowson (324) suggest that total body water is a more appropriate reference standard (than surface area) for comparing infant and adult renal function. Barclay *et al.* (325) state that "the present estimation of renal tubular reabsorption is a mathematical artefact and has little physiological significance." The existence of the material covered by this review is evidence of widespread disagreement. Russo *et al.* (326) give a statistical analysis of a number of renal functions in the dog.

Astarabadi & Essex (327) report that hypophysectomy prevents hypertrophy of the kidney following ureteroduodenostomy and contralateral nephrectomy in the dog. Constantinides (328) finds that stress in the form of formalin injection, cold or forced activity causes proliferation of the proximal convoluted tubules in rats; the effect is prevented by adrenalectomy. Goodman *et al.* (329) report on endocrine influences on proteinuria in the rat. Bucht (330) describes the changes which occur through pregnancy in renal function in correlation with measurements of cardiac output and plasma volume. Platt *et al.* (331) have determined the anatomical and functional effects of subtotal renal ablation. Goldman *et al.* (332) find proportional reductions of  $C_{CR}$ ,  $C_{PAH}$ , and  $Tm_{PAH}$  in patients with multiple myeloma.

Trabucco & Marquez (333) claim to have demonstrated that the glomerular tuft is an evagination of one wall of a single vessel.

Zinsser (334) considers implications of the transfer of the kinetic energy by the pulse wave to the tissues, stressing the similarity of the glomerulus to a hydraulic ram. This would not appear to fit with the lack of effect on renal function when pulse pressure is abolished.

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## EXCITATION AND CONDUCTION IN PERIPHERAL NERVES<sup>1</sup>

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The last few years have seen remarkable advances in our knowledge of the process of excitation, the study of ionic shifts and conduction in nerve fibers. The period covered by this review (June, 1952 to June, 1953) has been characterised by a stabilisation of advance and a rounding off of achieved knowledge. Research on saltatory conduction in myelinated nerve fibers is extending towards the study of conduction in the myelinated pathways of the central nervous system. Hodgkin & Huxley (80) have presented an admirable theoretical and quantitative description of membrane current and its application to conduction and excitation in nerve, which the reviewer considers as "the paper of the year." The structural aspects of nerves have led to renewed studies, making use of refined techniques.

A certain number of books and reviews on the subject have appeared, among which the following deserve attention: Bremer (19), Ciba Symposium (111), Eccles (41), Grundfest (60, 61), von Muralt (122, 123, 126), Nachmansohn (128 to 131), Stämpfli (150, 151), Tasaki (158), Tobias (162), and Wilson (169).

### THE STRUCTURE OF THE NERVE FIBER

For the understanding of the process of conduction in myelinated nerve fibers the pattern in the nodes of Ranvier is most significant and until today not clearly understood. Hess & Young (68, 69) have published papers in which the present situation is most ably reviewed and which contain at the same time valuable new material. The node of Ranvier is marked by a reduction of the diameter of the axon to less than half of the internodal diameter (large mammalian fibers). There is no visible transverse boundary across the axon at the node, but the cementing disk which surrounds the axon at the smallest diameter has a radial thickness of  $5 \mu$  in the largest mammalian fibers. This disk can appear as a transverse double contour, without being a boundary. Outside this disk is a perinodal space, bounded externally by the sheath of Key and Retzius. The authors estimate the area of the cylinder of axon membrane exposed at the node at  $4 \mu^2$  and the total area of the narrow portion of the axon at the node at about  $90 \mu^2$ . Methylene blue stains the whole narrow region suggesting that this may constitute the nodal membrane.

Gasser (58) has presented electron microscopical images as a preliminary, but none the less most interesting report. Working on C fibers he noticed that silver stained fibers appeared in cross section as black rings and not as

<sup>1</sup> The survey of literature pertaining to this review was completed in June, 1953.

black dots, as soon as care was taken that diffraction fringes did not print into the photographic picture. Silver is deposited on the surface of the fibers, thus producing a ringed appearance. Keeping the pH of the fixing solution (osmic acid) constant yields consistent findings from preparation to preparation. The axoplasm is filamentous, containing mitochondria and endoplasmic reticulum. The C fibers appear to be provided with an external circuit inside the Schwann sheath, whereas in medullated fibers the current flow outside appears to the author as a necessary condition for impulse conduction. The axon-sheath relation at the node of medullated fibers is most interesting. Attached to the free border of the axon at the node are fibrils anchored at their outer end to the Schwann membrane, which at the node turns inward to form a circular groove with a sharp apex. Throughout the internode mitochondria are to be found, but they are particularly dense in the vicinity of the node. The axon has two constrictions, one at the node and one at the mid-internode where it passes the Schwann nucleus. The study of the incisures in the myelin (Schmitt-Lantermann) has led Gasser to the belief that the conductivity across the whole internode would be approximately equal to the conductivity across the node. Hodler, Stämpfli & Tasaki (84) have measured the resistivity values and found for the myelin sheath of one internode 200 megohms and for the plasma membrane of the node 80 megohms.

Fernández-Morán (51, 52) has extended his work on the submicroscopic structure of nerve fibers and written a review (53). The myelin sheath can be regarded as a concentrically laminated tube, with an external fibrous membrane. The axon is a cylindrical fibrous core. The concentric layers in the myelin are composed of radially oriented rods, presumably lipids, bound together by a protein framework. The axolemma membrane represents the artificial accentuation of axon filaments, regularly found at the sheath-axon boundaries [see Baud (8)]. Myelinated and nonmyelinated fibers seem to have a common pattern of submicroscopic organisation.

The discussion whether the sheath is a barrier to penetrating substances or not is still going on. The older evidence has been reviewed by Stämpfli (150) and Lorente de Nó (105), diverging of course in their respective conclusions. The evidence against Lorente's ideas, that the epineurium is freely permeable to solutes, ionised or not, and that the electric resistivity is low, or to be more specific, equal to or lower than that of the interstitial spaces, and that removal of the epineurium and dissection of single nerve fibers are procedures which result in profound changes in the properties of the nerve fibers, is given below. The time of action of applied agents is shortened considerably by the removal of the epineurium. Chloral hydrate, cocaine, veratrine, glucose, methylene blue, potassium chloride, rubidium, barium, and calcium have been studied, and with radioactive isotopes the speed has been measured directly. Crescitelli (34) has developed a method of reversible de- and re-sheathing of a nerve and has shown that by restoration of the sheath the barrier properties return unaltered. Chloroform and *n*-amyl-carbamate are exceptions and seem to render the epineurium per-

meable. Lorente de N6 maintains (105) that the action of gases becomes maximal after 6 to 10 min., that the epineurium is not polarisable, and that it has no significant participation in electrotonic phenomena. He contends that removal of the epineurium discards only a small part of the connective tissue sheath of nerve, and that the major part is endoneural. With regard to the external concentration of sodium, Lorente de N6 draws the conclusion that it plays a rôle in nerve physiology only insofar as it regulates the internal sodium content and that a denuded nerve in a sodium-free medium loses its internal, loosely bound sodium. Further experiments on the rôle of the epineurium have shown that the serum of a cat has a marked effect on restoring the excitability of a frog nerve in an oxygen-free solution and that a desheathed nerve has properties different from those of a sheathed nerve [Aykut (6)]. Shanes (143) found that removal of the sheath produces a swelling in the fibers of bullfrog nerve (gain in weight 40 per cent in 3 to 4 hr.). The sheath is a barrier with complex properties and has a metabolic function which deserves further study (150).

Nordqvist (133) has used hyaluronidase on the sheath and studied the penetration of procaine. Hyaluronidase increases the speed of penetration and also the speed of recovery. On isolated bundles of nerves hyaluronidase has no visible action and the resting potential remains unchanged.

Sjöstrand (145) has studied the myelin sheath at a magnification of 160,000 and discovered an extremely regularly arranged system of concentric lines, uniformly spaced at 119 Å and running continuously around the sheath. The principal lines presumably represent protein membranes separated by the radially orientated lipid molecules. The spacing is a little larger than the data obtained by x-rays on fresh frog nerve [Elkes & Finean (42)].

There has been some discussion in recent years whether the central nervous system contains nodes of Ranvier or not. Recently [Hess & Young (68); Huxley & Stämpfli (89); Feindel, Allison & Weddell (48); Hess & Young (69); Allison & Feindel (1); Bodian (13)] renewed reports have proved that nodes are present, although they are not similar to those found in peripheral nerves. The axon is constricted (69) and myelin is interrupted; these points of greater permeability show a definite periodicity, which has been studied extensively (69). On central fibers of 3 to 15  $\mu$  diameter the spacing of the nodes is from 300 to 1700  $\mu$  and increases with fiber diameter, as in peripheral nerves, and also with growth of the animal. In new-born rabbits the smallest fibers have internodes of about 200  $\mu$ . These findings confirm the belief that conduction in myelinated fibers of the central nervous system does not differ much from conduction in peripheral nerves and is also saltatory. The staining properties of these nodes suggest that they are spots of high permeability.

#### EXCITATION AND CONDUCTION

*Saltatory conduction.*—Bullock (21) wrote in the *Annual Review of Physiology* for the year 1951, "Today, it is necessary to say that our gross picture of conduction in myelinated fibers has been more radically altered by one



saltation than by the progress of several previous decades. Huxley & Stämpfli (89) have obtained elegant direct evidence of the most telling kind that the earlier suggestions [of saltatory conduction] were correct." The present reviewer is quoting this statement, because he is aware (with a certain amount of distress) that some authors who have contributed further evidence for saltatory conduction in 1952 and 1953, have written their papers with a slight tendency to consider their own contribution as "a final proof" with a certain disregard of the basic importance of Tasaki's and Huxley & Stämpfli's work. It is most satisfying if an important new finding is confirmed by other workers who do not belong to the "group," and from a psychological point of view it is understandable that each ally has the feeling that he has been the one who decided the battle. It is the task of reviewers to put things back into the right order, and from this point of view the book of Tasaki (158), the review of Stämpfli (150), the paper of Hodler, Stämpfli & Tasaki (84), and the review of Frankenhaeuser (56) deserve special attention.

All myelinated fibers are subdivided into nodes and internodal segments, and the myelin sheath is interrupted at the node, which is the only place where a myelinated fiber can be excited [Tasaki (154, 155)]. In single isolated nerve fibers this can be shown with adequate electrodes of the bridge insulator, oil gap, or air gap type (150), but it has also been proved on the intact nerve trunk [Stämpfli & Zotterman (148); Lussier & Rushton (108); Frankenhaeuser (57)] where only the epineurium had been stripped.

The node is the only site where excitation takes place, and it is only at the node where inward flowing membrane currents have been observed [Huxley & Stämpfli (89); Stämpfli (150); Frankenhaeuser (57)]. If a myelinated single nerve fiber is excited close to the node and then at a distance, the curves representing the strength-latency relation are different. For both brief and long stimulating pulses, longer latencies were observed when the stimulating electrode was located farther from the node. This difference is related to the spread of the potential wave of the stimulus from the site of stimulation along the myelinated portion of the nerve fiber to the neighbouring node [Tasaki & Mizuguchi (155)]. This spread occurs at a finite rate, and therefore the rising phase of the action current is retarded continuously with increasing distance of the recording electrode from the proximal node. This fact is ascribed to the distributed capacity of the myelin-covered portion of the nerve fiber. Action currents, flowing through the axis-cylinder, and action potentials, recorded from the surface of the nerve trunk, show a difference in time-course which is attributable to this distributed capacity. The retardation of the action potential of a conducted nerve impulse increases continuously with the distance from the node. At relatively high temperature (20°C.) the velocity of conduction is determined to a major extent by the rate of spread of the potential wave along the internode with its distributed capacity. At low temperatures, however, it is probable that the rate of movement of sodium and potassium ions at the nodal membrane is the main factor determining time lag and, by that, conduction velocity.

At the node the steepness of the rising phase of the action potential shows a maximum [Hodler, Stämpfli & Tasaki (84); Stämpfli & Zotterman (148); Frankenhaeuser (57)], and it drops to a minimum between nodes. The variation in steepness is greater than 1:3. The "active" change in electromotive force across the excitable membrane of a myelinated fiber takes place only at the node, and the potential wave spreads with finite velocity along the myelin sheath of the internode. Nervous conduction in the myelinated fiber differs considerably from conduction of the activation wave in Lillie's model, where the steel wire was protected by glass tubes and where there is no leakage. Leakage of current through the myelin sheath in the nerve fiber is important, but the current density and the intensity of the electric field through the nodal membrane is much greater compared to the myelin sheath. The latent period of the action potential of a conducted nerve impulse varies continuously as the distance along the fiber, but a "new born" action potential arises only at each node. Conduction of the nerve impulse in myelinated fibers is saltatory with respect to space but not, in general, with respect to time [Tasaki & Mizuguchi (155); Hodler, Stämpfli & Tasaki (84)].

Additional evidence of saltatory conduction can be derived from the photochemical experiments on single myelinated nerve fibers with ultraviolet light [Booth, von Muralt & Stämpfli (16); Hutton-Rudolph (88); von Muralt & Stämpfli (127)]. The node is extremely sensitive to ultraviolet light of wave lengths less than 300  $m\mu$ , but the internodal region is very insensitive and shows no specific reaction with regard to wave length. The photochemical activity curve of the unexcited node was determined [Booth, von Muralt & Stämpfli (16)] and shows three maxima at 265, 280, and 297  $m\mu$ . At 265  $m\mu$  the excited node is 4.8 times more sensitive if irradiated with synchronised flashes of ultraviolet light (method of stroboscopic photochemistry) than if the flashes fall on it during the interval between two excitations. This phase effect of intermittent, synchronised irradiation is regarded as a proof that additional chemical events are taking place at the moment of excitation in the node [von Muralt & Stämpfli (127)]. At 280  $m\mu$  the phase effect is much smaller and shows a peculiar behaviour, which can be related to inactivation of enzymes important for the normal sequence of chemical events in the excited node.

Another aspect of saltatory conduction presents the study of rheobase and chronaxie on single nerve fibers. The chronaxie of the node is extremely low and can attain values of as little as 47  $\mu\text{sec}$ . [Sakamoto (140)]. In the internode the measured chronaxie is high. If the testing electrode (gap method) is displaced along the fiber, the chronaxie decreases linearly when approaching a node and increases with a jump to a maximum after passage of the node, because now the cathode is on the side of the next node and the anode is on the side of the node which has just been passed by the electrode [Hodler, Stämpfli & Tasaki (83)]. Further advance in the technique of microelectrodes was achieved by Tasaki (157) who recorded action potentials by inserting a microelectrode into the inside of myelinated nerve fibers. As a

result of unavoidable injury the values are low. By polarising single nerve fibers in the dorsal funiculus evidence of nodes was obtained, and by measuring the threshold as a function of distance the nodes could be located and were shown to be regularly spaced.

Narcosis experiments have been used first by Tasaki to demonstrate that the node is the only site where excitation and narcosis takes place. These experiments have been repeated [Wolfgang & van Harreveld (171)] together with blocking experiments with an air gap. The findings are reported by the authors as not supporting the theory of saltatory conduction.

The study of the initiation of propagated potentials in single nerve fibers [del Castillo (22)] has added new evidence to the now well-known fact that excitation takes place at the node. Saltatory propagation of excitation in all myelinated peripheral fibers is today a well established fact and it seems highly probable that the same is true for the myelinated fibers of the central nervous system. Direct experimental evidence is, however, lacking and will be so for some time on account of the very difficult technique.

*Nonmyelinated fibers.*—The remarkable series of papers on current-voltage relations in the membrane of the giant axon, on currents carried by sodium and potassium through the membrane, the conductance in the membrane, and the dual effect of membrane potential on sodium conductance by Hodgkin, Huxley & Katz (76 to 79) have been reviewed by Larrabee & Edwards (102) in this Review, and by Hodgkin & Huxley (81), but they are mentioned again on account of their fundamental importance. They have been extended by the theoretical paper on membrane current and its application to conduction and excitation in nerve (80). Hodgkin & Keynes have studied the mobility of potassium in giant axons (82) allowing internal potassium to exchange with externally applied labelled potassium  $K^{42}$ , but only in a restricted region. If such fibers are placed in oil after the exchange most of the labelled potassium remains inside, and the mobility of potassium can be measured by moving the fiber horizontally over a well shielded Geiger counter. The velocity with which the labelled patch moves under the influence of an electric field gives a value for mobility and the broadening of the patch a value for diffusion. Ninety per cent of the potassium in the axoplasm is free to exchange with labelled potassium. The average mobility was found to be  $4.9 \times 10^{-4} \text{ cm}^2 \text{ sec}^{-1} \text{ V}^{-1}$  and the average diffusion coefficient  $1.5 \times 10^{-5} \text{ cm}^2 \text{ sec}^{-1}$ , which corresponds to a 0.5 M KCl solution. Excitability of large and small nonmyelinated fibers of crab nerve (*Cancer magister*) have been studied [Easton (40)], using as a criterion the minimum energy utilization of square pulse stimulation, being a more natural index than chronaxie. Fibers producing small spikes are excited with small energy but require long duration (5 to 50 msec.) for minimum utilization. Fibers producing large spikes have a minimum energy utilization at short duration of stimulus (1 to 5 msec.). The question of the relation between fiber diameter and conduction velocity in non-myelinated fibers (squid giant axon) has been revised by Hodes (74) who found direct proportionality between

velocity and diameter with an increase of 6.5 m/sec. for a diameter increase of 100  $\mu$ , not confirming the previously established relation of  $v = \sqrt{D}$  ( $v$  = velocity,  $D$  = Diameter).

The repartition of respiratory enzymes in the tissue spaces of giant axons has been studied by Arvanitaki & Chalazonitis (7).

*Membrane and ionic transfer.*—The properties of the nerve membrane and its relation to conduction have been reviewed by Katz (91). There have always been objections to the membrane theory [see Beutner (12)], and it can be said that the membrane theory of excitation centers around an invisible structure. But the fact that potassium ions can diffuse freely within the axon and that there is an extremely slow exchange of ions between inside and outside is reliable evidence of a surface barrier. The fact that at any given level of the axon no measurable potential differences are encountered is a proof that the resting potential and the action potential are developed wholly across the surface membrane. It is noteworthy that Katz quotes Overton's paper in *Pflügers Archiv* of 1902 in which the nucleus of the "sodium theory" is contained and where Overton stated that "impulse conduction is accompanied by an exchange between intracellular potassium and extracellular sodium ions." Membrane potentials have been measured on single myelinated nerve fibers [Stämpfli (149)], the electroplates of the electric eel [Keynes & Martins-Ferreira (93, 94)], mammalian skeletal muscle [Ware, Bennet & McIntyre (164)], crustacean ganglion cells [Tauc (159)], and even on such primitive cells as the myxomycetes [Tauc (160)]. The findings on the electroplate of the eel (94) deserve special attention. Across both faces of the electroplate there is a resting potential of the same size as observed in other excitable tissues. During activity a large reversed action potential develops across the innervated face, while the potential across the nonnervous face of the electroplate remains virtually unaltered. The reversed potential is thus added to the unaltered potential, and each electroplate contributes during activity a voltage equal in size to its action potential. The nervous face is very sensitive to changes in sodium content of the surrounding solution, and treatment with sodium-free solutions abolishes the action potential without affecting the resting potential. The nonnervous face is insensitive, and sodium-free solutions produced only a slow decline in the size of the spike. Potassium, however, depolarised both faces of the electroplate. The authors make a very interesting suggestion with regard to the origin of electroplates. They think that they are specially adapted muscle fibers and not modified motor end-plates, as has been assumed until now.

The sensitivity of different fibers to lack of outside-sodium, studied on desheathed bullfrog fibers, showed that B fibers as a group are most sensitive, followed by the C and A fibers [Crescitelli (35)]. Lithium was the only substance found to be able to replace sodium in these reactions, and tetraethylammonium ion was without action in the absence of sodium. Fatt & Katz (46) have studied the effect of sodium ions using the intracellular re-

cording technique on neuromuscular transmission. The end-plate potential drops to subthreshold values if the external sodium concentration is reduced to one-fifth and block ensues. The electric reaction of the end-plate to applied acetylcholine is also affected by changes in sodium concentration. The authors develop an interesting theory according to which the entry of sodium ions releases acetylcholine from the nerve endings. This release can be regarded as a cation exchange process, analogous to the release of potassium ions from active nerve fibers. The block produced by sodium deficiency is similar to the block produced by lack of calcium. This is of special interest, because in the model of nerve activity suggested by Hodgkin, Huxley & Katz (75) the membrane is supposed to contain a calcium compound liberating a "carrier" capable of transporting a large number of sodium ions through the membrane. If acetylcholine ions are released in exchange for sodium ions, then the fact that a change of calcium concentration affects acetylcholine release in an aggregate manner, while a change of sodium concentration does so in continuous manner, becomes understandable. There is, however, the other possibility, that calcium-lack simply blocks the nerve impulse at a preterminal point, without affecting spontaneous activity of the terminals. A decision between these views is impossible today. Lansing & Rosenthal (101) have studied the relation between ionic transport and ribonucleic acid in the cell surface. There is a thin layer of ribonucleic acid on the cell surface of *Arbacia* eggs and *Elodea* cells which influences the uptake of calcium and strontium ions. Unfortunately no reference is made to the "carrier" hypothesis of the model of nerve activity.

Shanes (142) has developed the "potassium theory" and given a detailed account of slow time scale changes. Potassium release from a fiber under the influence of metabolic agents and "unstabilizers" of the same type of action as veratrine has been studied in detail. Oxygen lack, moniodacetic acid poisoning, potassium deficiency, and veratrine in small doses produce release of potassium and uptake of sodium. Glucose reduces the ionic transfer induced by oxygen lack, and moniodacetic acid counteracts this reduction. Low moniodacetic acid action is opposed to the veratrine effect. Shanes envisages alterations in potassium retention (a) as a modification of the intensity of metabolic "forces" effected by metabolic agents, or (b) as changes in permeability effected by stabilizers and unstabilizers. Shanes & Berman (144) have studied the penetration of potassium, sodium, chloride, and sucrose into intact nerve trunk of frog nerves. The "spaces" for sucrose are smaller than for chloride, but the "excess potassium space" equals the chloride space. If only  $\frac{1}{3}$  of the sodium is replaced by potassium, the water balance remains undisturbed; if the ratio is higher a large gain in weight occurs. The transfer through the membrane occurs in two stages, an initial rapid one, followed by a larger prolonged one. By microinjection, combined with internal microelectrode recording, internal ionic changes have been studied [Gundfest *et al.* (62)]. Blocking effectiveness is in the order  $K^+$  (50),  $Na^+$  (5),  $Ca^{++}$  (0.03),  $Mg^{++}$  (0.003) with the figures giving approximate

blocking dose in  $\mu\text{g}$ . There is a difference reported in the potassium/sodium ratio between conducting (nervous) tissues, where the authors find a ratio of less than unity and contractile (muscular) tissues, where it is reported to be greater than unity [Davies *et al.* (36)].

*Local responses (subthreshold activity).*—Rosenblueth (138) has given an extensive review on the local responses of axons, covering the literature up to 1952. Stämpfli (150) has pointed out that the term subthreshold activity should replace the old term "local response," because it is not an excitation of all-or-none type, taking place in an area too small to excite adjacent regions. Del Castillo & Stark (23) have studied the subthreshold activity of single medullated nerve fibers and confirmed the previous findings of Tasaki, Stämpfli, Huxley & Stämpfli, and Schoepfle & Erlanger [see (150)] on single myelinated nerve fibers. Nonpropagated subthreshold responses can be demonstrated following cathodic stimuli of near threshold strength at the nodes of Ranvier. They correspond to those observed in nonmyelinated nerve fibers and recorded from intact nerve trunks.

*Other aspects of excitation.*—Lullies (106) has published a review on laws of excitation and our conception of excitation in nerve. A specialised aspect of excitation by temperature is presented by Hensel (66) in his review on thermoceptor activity.

Threshold measurements on single myelinated nerve fibers with the bridge insulator method have shown that crushing of the fiber in the internode produces a lowering of threshold in the node which is two internodes away, and an increase of threshold up to unexcitability in the neighbouring nodes [Lüttgau (109, 110)]. The excitability of excised nerves shows fluctuations, which depend on the damping factor (*amortissement*) measured according to Monnier & Lavigne (115, 118). If damping is high in a nerve, the threshold of excitation is very stable, if it is lowered, by applying phosphate buffer or local rise of temperature, the threshold shows fluctuations and repetitive discharges are observed. Strychnine has hardly any action on a normal nerve, but if the permeability is changed by application of choline or if the metabolism is influenced by 2,4-dinitrophenol, instability is produced by strychnine. Monnier (116) has given a review of the phenomenon of the damping factor in nerve and its applications and has also reported on experiments in man (117). The rôle of the damping factor is evident if a nerve is studied on stimulation with alternating current. The curve relating frequency and threshold is a very broad resonance curve for which Monnier has introduced the term *pararesonance*. If the nerve is reduced in its calcium content (citrate or phosphate action) the curve is a real resonance curve with a sharp minimum at about 200 c.p.s. The damping factor is a measure of the stability of a nerve and is related to the resting potential, but has the advantage of being measurable without inserting electrodes into the nerve. Motor fibers show a different damping factor from sensory fibers, the latter having a more pronounced damping, i.e., stability.  $\text{CO}_2$  increases the damping, independent of pH change and acts on nerve metabolism, and if damping



is low, repetitive discharges in nerve fibers are started. Similar findings are reported by Müller (120, 121), Laget (98), Legoux (103), Laget & Saumont (99) and Sato (141). Repetitive discharges in roots of abdominal ganglia can also be produced by a single impulse in the central giant fiber of the crayfish [Wiersma (165)]. The fiber showing repetition is usually also spontaneously active. Blocking the synapse with nicotine leaves the spontaneous activity unaltered. Fatt & Katz (45) have found that end-plates of resting muscle fibers are the seat of spontaneous electric discharges, which are "miniature end-plate potentials" and occur at normal synapses. There is a random succession of such potentials with an amplitude of the order of 1/100 of the normal end-plate response. They are reduced by curarine, increased in size and duration by neostigmine (prostigmin), and abolished by denervation or anesthesia. The frequency varies, increasing with temperature and strikingly so with small increases of osmotic pressure. Sodium deficiency reduces the amplitude of these potentials, and calcium deficiency acts in steps, involving all-or-none blockage of a variable number of these components. Katz is of the opinion that thermal agitation of ions across the nerve membrane plays an important part and that the miniature potentials are attributable to local excitation of areas concerned with the release of acetylcholine. Repetitive discharge of impulses after treatment with sodium citrate occurs in the dorsal root ganglion [Dun (39)] as a result of mutual reexcitation of the nerve fibers.

In a discussion on excitation and inhibition Fatt & Katz (47) have concluded that the end-plate potential arises from a membrane reaction which differs from the reaction associated with spike activity in two ways: (a) it is induced by acetylcholine and (b) it involves depolarisation of a membrane by short-circuit and not a specific increase of sodium permeability which leads to a reversal of the membrane potential. Fessard (54) has given an account on the wide diversities of synaptic properties as exemplified in electric organs, and Granit (59) dealt with excitation and inhibition in the retina.

Failure of conduction after injury spreads as degeneration proceeds from the proximal end (near the injury) to the distal part. At the same time the myelin retracts from the nodes, and this nodal retraction also spreads from the site of the crush or cut. Failure of conduction is related to the increase of the naked axon area at the node [Causey & Stratmann (24)].

Mühl & Henatsch (119) have studied the refractory phase of single myelinated nerve fibers and the increase in time by cathodal- and decrease by anodal-electrotonus. Laget (100) reports on the variations of potentials in mammalian nerves during anoxia and Legoux (104) on adaptation to currents of long duration and the reversal of depolarisation produced by oxygen lack and potassium action by anodal currents. Temporal and spacial facilitation in the electric cell has been studied [Altamirano-Orrego *et al.* (2)]. Excitability of sympathetic centers was measured by Chauchard & Chauchard (29, 30, 31).



*Physical properties and actions of physical agents.*—Bryant & Tobias (20) have continued the effort to relate excitation to other changes in physical properties such as have been described by Hill [volume change (73) and shift of water (72)] and Hill & Keynes [opacity change (71)]. The results of measuring scattered light from excited nerves are somewhat unsatisfactory, because the reaction is complex and not reproducible for the same type of nerve. There is an optical effect related to activity but stretch has also an influence on the measurements, and the change of scattered light not only depends in size on the state of tension under which the nerve is suspended, but even in sign (decrease of scattered light in a lax nerve, increase under stretch). The authors are also very careful in making a definite statement that the mechanism underlying the optical change is a constant accompaniment of impulse propagation. The important question of electrical resistance change during the production of the action potential of myelinated nerve has been investigated by Fabre (43, 44), with a new amplifier set-up, but most unfortunately not on single nerve fibers, but on whole nerve including the sheath. The unorthodox results reported by the author must be considered as a contribution to the sheath problem. Redox-potentials have been measured in normal and degenerating nerves of the mouse and rabbit by *in vivo* injection of dyes [Willème (166)]. In the course of degeneration, the redox-potential decreases from rH15 to rH4.5 after 9 days. An interesting report is that of Mazoué, Chauchard & Busnel (113) on excitation by ultrasonics, independent of course from thermal action. Threshold and time-intensity relations correspond to the classical law of Weiss and a "piezobase" is defined. The duration of excitation by ultrasonics reaches a limiting value above threshold, but with increasing intensity this limiting value increases up to a maximum. Schneider (147) has studied the elasticity and mechanical resistance of single myelinated nerve fibers which are specially protected at the node and can stand considerable stress without rupture or loss of conduction. In the internode, elongations up to 30 per cent can be withstood without block in conduction. The sheath plays an important part in the total mechanical resistance of a nerve. The node is the most resistant part in a single nerve fiber. Changes in the action currents of single nerve fibers, produced by pressure changes of high frequency have been reported by Keidel & Kern (92).

*Models and mathematical treatment.*—Studies on nonlinear impedance characteristics of dynamically variable membranes are announced by Schmitt (146), and Strohl and Pellerin (153) have treated a new type of core-conductor and studied the appearance and propagation of the potential variation on the surface of nerve [Strohl, Ubersveld & Pellerin (152)]. Too little known among neurophysiologists are the model studies of Bonhoeffer and his group [see (14, 15)], especially with respect to a new saltatory model, realised by Frank (55), with which he gives a very interesting explanation of the high potentials obtained in the electric organs. The model experiments of Yamagiwa (172) may be recalled at this point.

## RÔLE OF ACETYLCHOLINE

Nachmansohn and his colleagues [see (128 to 131)] have accumulated an increasing number of pertinent facts about the rôle of acetylcholine in excitation and conduction in nerve fibers. It might be interesting to compare the existing evidence with hypothetical evidence one would wish to possess as a fundament of a theory. (a) The first prerequisite would be the proof that, closely connected with excitation, each action potential in nerve is accompanied or preceded by the release of a minute amount of acetylcholine. (b) If acetylcholine is responsible for the changes occurring in the membrane, or closely related to them, the speed of liberation and of destruction must be high. (c) Microinjection of a small amount of acetylcholine at the appropriate site should produce a noticeable effect, either depolarisation or repolarisation. (d) By blocking acetylcholinesterase it should be possible first to increase the excitatory process (small accumulation of acetylcholine) and then to block it and possibly to reverse the sequence by deblocking acetylcholinesterase.

It is only fair to say that in the course of the last years Nachmansohn and his colleagues have come pretty close to proving most of these prerequisites. The technical difficulties are great and should be respected by those who criticize the evidence for the "acetylcholine-theory." In this review only the experiments of the year are quoted.

Acetylcholine is liberated as a consequence of stimulation of small motor nerve fibers of the frog [Brecht & Holler (18)]. Care was taken that only fibers of 4 to 8  $\mu$  carried impulses to the muscle, and the acetylcholine was determined in the perfusate. Chagas (27) showed that the acetylcholine content of the main organ of *Electrophorus* decreases markedly after indirect stimulation and is resynthesized at rest. Direct stimulation of the organ reduced the acetylcholine content only very little. (*Electrophorus* has only 5  $\mu\text{g./gm.}$  of acetylcholine in contrast to *Torpedo* with 40 to 100  $\mu\text{g./gm.}$ ).

Wilson & Cohen (170) have pointed out that experiments in which the complete blocking of acetylcholinesterase was determined on homogenised tissue might be erroneous. There is always a marked difference in the concentration of the anticholinesterase between the outside and the inside, so that by contamination in the homogenate a block of the enzyme, which might not have existed before, can be produced during homogenating. All experiments trying to show that nervous conduction existed in the absence of active enzyme are subject to this criticism. The authors used dimethylaminoethyl acetate (DMAEA) instead of acetylcholine. This compound is able to reach sites of acetylcholinesterase which are protected from quaternary ammonium salts and is hydrolysed there. They distinguish "outside esterase" (reached by neostigmine), which is not essential for conduction, from "internal enzyme," the relation being about 1:3. Neostigmine, tetraethyl pyrophosphate, and decamethonium nearly completely inhibit external enzyme. Those enzyme inhibitors, which block conduction (di-isopropyl

fluorophosphate and eserine) inhibit external and internal enzyme. Conduction stops when the enzyme activity falls below 20 per cent. The binding forces of acetylcholinesterase have been studied by Wilson (167) who has also studied the reactivation of alkyl phosphate-inhibited enzyme (168). Bergmann & Shimoni (10, 11) reported on the inhibitory effects of quaternary ammonium salts and the effect of pH and the rôle of cholinesterase in the conductive process (9). Hellmann (65) using the method of Koelle for histochemical localisation of cholinesterase published selectively stained images of end-plates.

Central excitation and inhibition has been reviewed by Feldberg (49) in the light of chemical transmission by acetylcholine. Three possibilities are discussed: (a) over-depolarization could produce inhibition, (b) release of acetylcholine at different parts of the same cell could have different actions, (c) release of acetylcholine could have opposite effects at different synapses. Strong and persistent depolarization by acetylcholine produces an electrotonic spread of depolarization current to adjacent parts, thus forming a barrier for the spread of excitation. Feldberg is inclined to think that this mechanism, observed under experimental conditions, does not apply for physiological conditions of central inhibition. The second possibility involves the assumption that the effect of acetylcholine is related to its locus of arrival on the surface. The third possibility is in conformity with the pharmacological evidence that acetylcholine can have opposite effects on apparently similar structures. A fourth possibility that there is a special chemical mediator for inhibition is discussed. The difficulties opposed to a uniform acetylcholine-hypothesis have also been dealt with by Heymans (70) who reminds us of precious advice given by Gowland Hopkins: "Any dogmatic teaching about any process of life is able to be checked by the fact that the living cell is above all a heretic."

An important series of papers are quoted here, because they are apt to throw new light on the mode of action of acetylcholine, although they are not directly related to excitation and conduction of peripheral nerve: Perry (134), Feldberg, Gray & Perry (50), Perry & Talesnik (135), Douglas & Gray (38), Hutter (86, 87), and Peters & Wakelin (136).

#### OTHER AGENTS

In the search for substances responsible for the energy supply in the restoration process following activity of a nerve, attention has been drawn to L-glutamate and glucose, both substances being essential to prevent loss of potassium from slices of rabbit and guinea pig brain cortex [see Turner, Eggleton & Krebs (161)]. Aspartate, but no other amino acids, can replace glutamate and glucose is always essential. Korey (96) has studied the rate of entry of radioactive potassium into brain slices and did not detect any change produced by glutamate or aspartate. A new aspect of the ionic environment of a nerve and its dependence on hormonal factors has been presented by

Cerf (25, 26). Adrenalectomized frogs showing adynamic symptoms were studied, and on their isolated nerves the following changes were noted: decrease of conduction velocity exaggerated by fatigue, increase of threshold, decrease of size of the spike, and increase of refractory period. If these nerves, are treated with isotonic sodium chloride or Ringers' Solution an almost complete restoration occurs. This is a new contribution to the "sodium theory," but strangely enough lithium cannot take the place of sodium in this restoration effect. Choline chloride has also a beneficial effect but only during 45 to 60 minutes, and afterwards the symptoms of sodium lack reappear. Other factors in addition to sodium lack must play a rôle. Thiamine seems to be another partner in the sequence of chemical events and has been studied by Andral & Blaizot (3, 4). They discuss two possibilities: (a) thiamine applied from outside liberates acetylcholine; (b) resynthesis of choline and acetate is favorably influenced by thiamine and cocarboxylase. Indirect evidence of the importance of thiamine can be derived from the observations of von Muralt & Zotterman (124, 125) that the activity of taste receptors (water taste of the frog) in the tongue can be blocked by application of antithiamine in aqueous solution (extracts from the intestine of the carp or from fern).  $\text{CO}_2$ -action on nerve was measured on whole nerve [Niedergerke (132)], on desheathed nerve [Coraboeuf & Thieulin (32)] and on isolated single myelinated nerve fibers [Coraboeuf & Niedergerke (33)]. There is clear evidence that the  $\text{CO}_2$ -action, which raises the threshold, is independent of pH-action and is a specific effect related to the metabolism of nerve. Adenosinetriphosphoric acid (ATP) has been discussed in connection with nerve metabolism, and Holton & Holton (85) have obtained spectrophotometric evidence that the perfusate of the isolated rabbits ear contained in the outflow, after stimulation of the great auricular nerve, an increased amount of a substance absorbing ultraviolet light between 255 to 265  $\mu$  [see (127)]. The possibility must be considered that ATP or some similar substance is a chemical transmitter [see also (64)].

#### FUNCTIONAL INTERRELATIONS AND CENTRAL ASPECTS

Three remarkable books have appeared, one by Eccles (41), another by Bremer (19), and a symposium on the spinal cord (111), which contain a number of references to the subject of this review.

The differences in diameter and other properties of nerve fibers have always attracted much interest since Gasser's fundamental paper on this topic. Lundberg (107) found that the sequence of blocking action of potassium ions is in a definite order: B fibers, delta, gamma, fast A, and C. Anoxemia showed the same sequence. The depolarization of the membrane at the moment of block was in large A fibers, 16 per cent of the normal value, in B fibers, 10 per cent, and in C fibers 29 per cent. By isolating single fibers from skin nerves of the toad and the cat Maruhashi, Mizuguchi & Tasaki (112) found the following groups: Toad: (a) tactile fibers, 8 to 15  $\mu$  diameter, receptive field 3 to 10 spots, adapts quickly to stimulus; (b) pressure fibers

4 to 5  $\mu$  diameter, receptive field 1 to 5 spots, adapts slowly; (c) nociceptive fibers, 3 to 9  $\mu$  diameter, receptive field densely distributed (d) unmyelinated fibers, subserving the perception of heat, cold, and mechanical stimuli. Cat: (a) tactile fibers, 8 to 14  $\mu$  diameter, receptive field 1 to 2 spots, adapts quickly; (b) pressure fibers, 3 to 5  $\mu$  diameter, receptive field spot-like, adapts slowly; (c) nociceptive fibers, 3 to 11  $\mu$  diameter, receptive field 2 to 9 mm<sup>2</sup>, impulse discharge phasic; (d) cold fibers, 1.5 to 3  $\mu$  diameter, receptive field punctiform, endings insensitive to mechanical stimuli; (e) wide-receptive fiber, 2 to 5  $\mu$  diameter, receptive field ranging from 1500 to 4000 mm<sup>2</sup>, sensitive to all kinds of stimuli; (f) afferent fiber, associated with the hairs, 6 to 12  $\mu$  in diameter, innervates large number of hairs, area 100 to 500 mm<sup>2</sup>; (g) afferent fibers of the subcutaneous tissue; (h) fibers connected with scratching, but not to pressing; (i) unmyelinated fibers subserving perception of heat and mechanical stimuli. Kobayashi, Oshima & Tasaki (95) have studied with a similar technique the afferent and efferent systems in the muscle nerve of the toad and the cat. Boyd (17) reports on nerve impulses from proprioceptors of the knee joint, Kuffler (97) on organisation, inhibition and excitation problems of the neurons in the retina, Hensel (67) on afferent impulses from cold receptors, and Tasaki & Fernandez (156) on the modification of cochlear microphonics and action potentials by KCl-solutions and direct current. The rôle of specialised nerve terminals in cutaneous sensibility is described by Hagen *et al.* (63).

Stimulation of the vestibular system and of the dark adapted eye produces a change of chronaxie of the motor fibers [Mies (114)]. Maximum conduction velocities of motor fibers in human subjects seem to depend on age and on the distance over which the impulse must travel (growth) [Wagman & Lesse (163)]. A posthumous paper by Renshaw, together with Rosenbaum (137) has appeared dealing with the excitability changes that injury to a motor axon produces in the motoneuron soma. The authors come to the conclusion that that injury under properly controlled conditions does not produce such a change. Dolivo, Fleisch & Infantinella (37, 90) maintain that section of the motor roots on one side, excluding carefully all other influences, modifies the response of the other side. Rudolph (139) reports also an increase of response even by application of urethane and polarisation in the periphery.

Herring gulls, maintained in a cold environment show conduction in the nerves of the metatarsal part of the leg at low temperature as well *in vivo* as *in vitro* [Chatfield, Lyman & Irving (28)]. There is a mechanism of adaptation of nerve conduction to cold which remains to be studied.

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# SOMATIC FUNCTIONS OF THE CENTRAL NERVOUS SYSTEM<sup>1</sup>

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## BOOKS AND REVIEWS

This year has been marked by the appearance of a number of books of considerable importance to neurophysiologists. In two of these the authors present a review in retrospect of their own scientific and philosophical development. Eccles (1) projects from his tremendous background of information concerning interneuronal relationships in simpler systems into hypothetical considerations concerning cerebral function and the relationship between brain and mind. Gellhorn's (2) remarkable compendium of neurophysiological information is directed toward the application of neurophysiology to neurology and psychiatry. The Cold Spring Harbor Symposium entitled, "The Neuron" (3), contains many valuable contributions. Spiegel & Wycis (4) present a description of a human stereotaxic technique and a stereotaxic atlas of the human brain. Bremer's lectures at the University of London have appeared in book form (5). Physiologists as a whole owe their thanks to the Bibliography Section of the Technical Information Division of the Library of Congress and to the Biological Science Division of the Office of Naval Research for making possible the production of annotated bibliography dealing with the physiology of the circulation of the brain (6).

A thoughtful commentary on the present status of cytoarchitectonics has appeared [Clark (7)]. Reviews and symposia on the following subjects have appeared: neuronal function at the axonal level [Rosenblueth (8); Stampfli (9)]; synaptic transmission [Bremer (10)]; excitation and inhibition (11); energetics of sensory receptors (12); the physiology of thermal reception [Hansel (13)]; olfactory function [Gerebtzoff (14); LeMagen (15)]; the oscillographic analysis of sensory responses of the cerebral and cerebellar cortices [Bremer (16)]; visceral, motor, and emotional functions of the limbic lobe [Colle (17); Gastaut (18); Dell (19); MacLean (20); Ingram (21)].

## STUDIES OF THE INPUT SIDE OF THE SYSTEM

*At the receptor level.*—The mechanism of receptor function continues to present unsolved problems. Easton (22) has related the fiber diameter to the duration of pulse which stimulates with minimum energy utilization. The results suggest that small fibers have a less efficient mechanism for

<sup>1</sup> This survey is based upon publications which were made available to the reviewer during the period extending from June, 1952 through June, 1953. Limitation of space has dictated the elimination of some material. Because of their wide availability the reviewer has elected not to include material appearing in abstract form in the Proceedings of the meetings of the American Physiological Society, the American Association of Anatomists, and The Physiological Society.

accommodation thus rendering them more susceptible to stimulation by prolonged potentials generated by receptor organs. Subthreshold mechanical stimuli delivered to pacinian corpuscles have been shown to result in the production of a local response which is a necessary intermediate between the receptor response and the resulting action potential [Alvarez-Buylla & Ramirez de Arellano (23)]. Cutaneous receptors are strictly analogous to carotid body receptors insofar as their responses to acetylcholine and  $\alpha$ -lobeline are concerned [Douglas & Gray (24)]. It is concluded that responsiveness to these agents cannot be taken as evidence of the existence of a synapse in the region of the receptor. A thorough and detailed analysis of the behavior of thermal receptors under various conditions of temperature stimulation has been presented [Hensel (25)]. It would appear that fibers from specific cold receptors have been found, and the role of the cold receptor in temperature regulation is discussed [Hensel (26)].

The potential difference across the eye has been found to be sensitive to metabolic poisons and is thought to be the result of electrochemical processes at the boundaries between the retina and the chorioid [Noell (27)]. The structural changes induced in the retina by iodoacetate poisoning have been described (28). Von Euler & Söderberg (29, 30) describe slow potential changes from the respiratory center which respond to chloralose and to carbon dioxide in such a fashion as to suggest their origin from medullary chemosensitive receptors.

*Transmission pathways.*—Peripheral areas of distribution of dorsal root filaments in the cat and the monkey have been found to be arranged in orderly, consecutive fashion within the dermatome, showing shifting overlap between successive filaments [Kuhn (31)]. Adopting one of the newer graphic art techniques, and departing from the usually vapid mode of presentation of results, Mountcastle & Henneman (32) and Rose & Mountcastle (33) present their studies of the thalamic tactile region in the rabbit, cat, and monkey. On the basis of histological and cytoarchitectonic characteristics the ventral thalamic group of nuclei is divided into three complexes: the ventrolateral, the ventromedial, and the ventrobasal. The ventrobasal complex appears to be that region in which tactile impulses from the head and body are relayed to the first somatic area. A study of the phyletic development of the nuclei, coupled with experimental findings, suggests the possibility that the ventromedial complex is concerned with gustatory and interoceptive sensibilities while the ventrolateral complex is related to the control of motor activity. No evidence for the thalamic zone relaying impulses to the second somatic area is available. The pattern of degeneration in a human thalamus following practically complete hemidecortication is described [Powell (34)]. A study of the form and distribution of the electrical field evoked in a thalamic relay nucleus by a single volley in a peripheral nerve in decorticated animals leads to the conclusion that the initial positive phase of the response arises from activity at the terminals of the lemniscus axons [Hunt & O'Leary (35)]. The thalamic responses to the activation of A-alpha, A-delta, and C-fibers have been differentiated [Schricker & O'Leary (36)].

A new spinocerebellar relay nucleus has been described in the lateral funiculus of the first and second cervical segments of the cat's spinal cord [Rexed & Brodal (37)]. Microelectrode recordings from within the body of the nucleus cervicalis lateralis indicate that it is most readily activated by low threshold cutaneous afferents and that the afferent impulses are synaptically relayed at cord levels caudal to the nucleus [Rexed & Ström (38)]. Anatomical studies (39) indicate that the afferents to this nucleus arise from all levels of the spinal cord, are both crossed and uncrossed, and probably constitute collaterals of coarser ascending fibers.

True to advanced billing (40), the anatomical description of a new pathway which may be predominantly tactile and to a lesser extent proprioceptive in function has appeared. Brodal & Walberg (41) describe degeneration in the motor and sensory areas of the cerebral cortex, in the cerebral peduncles, in the pyramids, and in the pontine gray matter following spinal cord lesions in the areas of the lateral and ventral corticospinal tracts. An electrophysiological investigation of this pathway is forthcoming (42). It remains to be seen whether the action potentials evoked in the motor cortex by peripheral nerve stimulation [Malis, Pribram & Kruger (43)] are transmitted over this pathway.

The activity patterns in single units of the auditory thalamic relay nucleus have been studied with a microelectrode technique. It has been found [Rose & Galambos (44)] that the thalamic neurons activated by click stimuli are confined to the pars principalis of the medial geniculate body in which the response consists of both spikes and slow waves. No firm correlation has been observed [Galambos *et al.* (45)] between stimulus intensity on the one hand and latency of slow waves, amplitude of slow waves, latency of spikes, frequency of spikes, and number of spikes in an individual discharge. While any single unit might respond to both ears or to either ear alone, the contralateral ear appeared to be somewhat more effective. Pure tones [Galambos (46)] initiate an "onset" response which resembles the response to a click stimulus and which is followed by a continuous discharge of the unit. An analysis of the responses to pure tones failed to reveal any clue as to the neural correlates for pitch discrimination or for loudness discrimination.

The complexity of function of the thalamic relay nuclei is also attested to by the results of a study of unit discharges in the simpler visual system [Bishop, Jeremy & McLeod (47)]. Electrically initiated volleys in the optic nerve give rise to an initial discharge of lateral geniculate neurones followed by secondary repetitive discharges which are selectively susceptible to anesthesia and asphyxia. The possibility is considered that recurrent collaterals from the radiation fibers enter into closed circuit relays with small cells in the nucleus.

Kuffler (48) has carried out an extensive analysis of the discharge patterns from ganglion cells of the unopened cat's eye. The receptive field and the organization of the receptive field related to a single ganglion cell is described. It is found that the discharge patterns from individual ganglion cells are not fixed and that interaction of different regions within a single

receptive field may occur. The discharge pattern of a single ganglion cell, set up by illumination of an entire receptive field, depends upon the summed effects of interacting pathways converging on the cell. Under diverse conditions of illumination the balance of active inhibitory and excitatory contributions changes within the same receptive field. Thus,

it is difficult to think of information content in terms of single unit contributions. One may rather have to consider that groups of fibers modulate activity levels in patterns by superposition or subtraction. The latter—for instance, transient cessation or diminution—is likely to be as meaningful as the opposite in terms of message content. Further, similar discharge patterns of different background illumination may convey a different meaning since they are superimposed on a different background activity.

The results are regarded as indicating that a one-to-one agreement between discharge patterns and information should not always be expected.

Evoked potentials have been recorded from the anterior and medial aspects of the pyriform area as a result of stimulation of the lateral olfactory tract [Ward (49)]. In addition, a high amplitude, prolonged, surface-negative "field spread potential" may be recorded from all parts of the head and appears to be independent of impulse transmission out of the lateral olfactory tract. Electrical stimulation of the intact chorda tympani nerve [Rosen (50)] is reported to give rise to homolateral facial contraction and pain in the region of the ear. None of the individuals tested reported the sensation of taste, even though subsequent section of the nerve was followed by a complete loss of taste on the homolateral anterior two-thirds of the tongue. These findings are in keeping with Harris' (51) contention that the sensation of taste is dependent not only upon the stimulation of taste buds and gustatory nerve fibers but is also dependent upon associated general sensibility of the surface of the tongue supplied by branches of the trigeminal nerve.

The transmission pathway for the pain sense has been the subject of several communications. Using the method of remaining sensitivity, Van Harreveld & Smith (52) find that some dermatomes in the cat undergo shrinkage when tested by painful stimuli following the removal of a sympathetic chain, indicating that afferent fibers from skin structures traverse the sympathetic chain. Pain thresholds to thermal radiation vary over different portions of the body (53). Landau & Bishop (54) have contributed an extensive study of pain sensibility employing a differential pressure block of A-delta fibers and a differential procaine block of C fibers. A study of Golgi preparations of human infants and newborn cats [Pearson (55)] suggests the existence of two spinal cord pathways for pain, one through the gelatinous substance to the nucleus proprius of the dorsal horn, another by-passing the gelatinous substance to terminate on neurons of the nucleus proprius. A state of altered cutaneous sensibility resembling causalgia in the human develops as the result of injection of alumina cream into the spinal cord [Kennard (56)]. A study of the responses to painful stimulation of exposed tendons [Yoss (57)] indicates that deep pain is transmitted via the lateral spinothalamic tract in the monkey and reveals certain features concerning



the lamination within this tract. Relief from intractable facial pain has been derived from the production of electrolytic mesencephalic lesions in the human (58).

Extending the results of the previous study of the cat (59), French, Verzeano & Magoun (60) describe the input, conduction characteristics, distribution, and projection of a medial corticopetal system in the monkey which may be regarded as the ascending reticular activating system in this animal. This extralemniscal sensory system appears to be most remarkably sensitive to the effects of anesthetics and other depressing agents (61), and the suggestion is made that such depression participates in the production of the anesthetic state<sup>2</sup> [see also (201, 202)]. The existence of multiple spinal projection pathways for both superficial and deep sensibility is suggested by the observations of Morin (63) and of Gardner & Haddad (64). These investigators find that bilateral responses of both the midbrain tegmentum and the cerebral cortical somatic areas continue to be evoked by electrical stimulation of superficial and deep sensory nerves in spite of spinal cord transections which involve all but one ventrolateral funiculus.

*Reception and perception.*—Questions concerning the identification of specific receiving areas of the cerebral cortex have interested two investigators who have used the evoked potential technique in anesthetized animals. Mickle & Ades (65) find that activity of auditory, vestibular, and somatic origin produces evoked potentials in the inferior portions of the anterior ectosylvian, suprasylvian, and composite gyri in the cat. They ask whether this polysensory projection area may not serve the function of correlation of sensory discharges relating to posture and spatial orientation. Tunturi (66) confines his observations on the auditory cortex of the dog. He describes an intensity gradient within each of the middle ectosylvian bands which is revealed by stimulation of the ipsilateral but not the contralateral ear.

Techniques of stimulation and ablation have also been applied to an analysis of cortical receiving areas. The ability to discriminate fine differences in roughness has been suggested as a function of somatic II in the cat [Zubek (67)]. Although it is commonly observed that the sensation of pain is not produced by stimulation of the somatosensory area in the unanesthetized human, pain reactions are now reported to have occurred upon such stimulation in individuals suffering from chronic persistent pain states (68, 69). Ablation of the cortical areas giving rise to these responses produced significant alteration in the pain syndrome. A study of 72 cases of traumatic ablation of the striate cortex [Spalding (70)] has permitted a correlation of the location of the striate injury with the visual field defect produced thereby. Macular vision is said to be represented unilaterally.

Auditory frequency discrimination is found to be independent of tonotopic organization within the auditory cortex of the monkey [Evarts (71)].

<sup>2</sup> Unpublished observations of Livingston & Haugen confirm this observation, utilizing stimuli to the teeth of cats which are presumed (62) to give rise to pure pain sensation.

In the same species, the ablation of the auditory cortex reduced but did not abolish the ability of the animal to perform auditory-visual associations [Evarts (72)]. On the other hand ablation of the prestriate cortex left this same association function unchanged [Evarts (73)]. The time required for the integration of a motor reaction to visual stimulation has been compared with the time required to produce an alteration in the alpha rhythm [Walsh (74); Stamm (75); Monnier (76)]. The two times appeared to be measures of activity in essentially independent systems. The evidence available does not support the possibility that the alpha rhythm "scans" the striate area (74). A preliminary note suggesting a new mechanism to account for the ability of the visual cortex to discriminate patterns has appeared [Sholl & Uttley (77)]. The porpoise [Kellogg & Kohler (78)] and mice of the genus *Peromyscus* [Dice & Barto (79)] are capable of perceiving ultrasonic sounds.

#### STUDIES OF THE OUTPUT SIDE OF THE SYSTEM

*At the spinal level.*—A number of studies concerned with the electrical activity of the spinal cord (80 to 84), the excitability of spinal motor neurons (85, 86), mechanisms of synaptic excitation and inhibition (87 to 90), and a new cytoarchitectonic analysis of spinal cord structure (91) deserve careful attention but are not germane to the subject of the present review.

The description of the gamma efferent system [Leksell (92); Hunt (93)] has continued to have a beneficial influence on our progress in understanding proprioceptive spinal reflexes. Gastrocnemius medialis, soleus, and tibialis anterior in the cat have been analyzed with respect to their muscle spindle content [Hagbarth & Wohlfart (94)]. The gamma efferents to muscle spindles have been found to be tonically active in decerebrate and lightly anesthetized animals [Granit & Kaada (95)]. This tonic activity could be accentuated by stimulation of the diencephalic reticular facilitatory system, the motor cortex, the pyramidal tract, the anterior lobe of the cerebellum, the habenula, and the medial portion of the head of the caudate nucleus. Inhibition of tonic activity followed stimulation of the bulboreticular inhibitory system and the anterior lobe of the cerebellum, the motor cortex, the orbital gyrus, and the amygdala. Tonic activity may be of such a magnitude that its elimination by de-efferentiation produces alterations in the facilitation of monosynaptic reflexes following upon stretch [Granit & Ström (96)]. The elicitation of the pinna reflex produces alterations in gamma efferent discharge [Granit, Job & Kaada (97)]. It is found that at low levels of motor neuron excitability and low levels of initial tension, stretch of an isolated muscle strip produces a reflex contraction which is confined to that strip. The remainder of the muscle may become involved in the reflex discharge if the background level of motor neuron excitability is sufficiently high [Cohen (98)]. It would appear that intense afferent activity from stretch receptors is not followed by post-tetanic potentiation of the spinal monosynaptic reflex [Ström (99)]. Afferent discharges from muscle spindles can produce discharges of motor neurons to the same muscle and facilitate the monosynaptic responses of the same and synergistic muscles [Hunt (100)].

These reflex activities accompanying excitation of muscle spindles must apparently be differentiated carefully from the reflex activities initiated by excitation of tendon organs (100). Tendon organ activation inhibits motor neurons to the same and synergistic muscles and facilitates the responses of antagonists. It would appear probable that these tendon organs discharge over afferents which Laporte & Lloyd (101) have found to be responsible for a disynaptic "inverse myotatic reflex mechanism." The results of Job's experiments (102) caution against the hasty conclusion that autogenetic inhibition may result solely from the excitation of tendon organs. He finds that autogenetic inhibition of gastrocnemius and quadriceps motor neurons elicited by stretch of a muscle which has become cooled, cyanotic, and congested is accompanied by simultaneous facilitation of antagonistic motor nuclei. This reaction resembles the reflex behavior resulting from the selective stimulation of C and A-delta fibers in the medial gastrocnemius and deep peroneal nerves. He concludes that the reversal in this reflex picture which occurs in the decerebrate animal is dependent upon the difference in tonic facilitatory influences from higher centers in the two types of preparations.

It has been found that a test stimulus delivered to a motor nerve will elicit discharges from synergistic motor nuclei provided these synergistic motor nuclei are in a sufficiently high state of facilitation [Job (103)]. Electromyographic and monosynaptic methods of testing reflex excitability have been compared and have been found to be at variance under certain conditions [Granit & Job (104)]. In a study of reciprocal inhibition and facilitation of antagonistic muscles around the ankle joint the reciprocal effects of ankle flexion and ankle extension were found to be highly asymmetrical [Granit (105)].

Magladery and his co-workers have now included patients with lesions of the central nervous system in their extensive study of human monosynaptic reflexes. In patients with cerebral or upper brain stem lesions the distribution of monosynaptic reflexes elicitable by single volleys did not differ from that in the normal, but recovery of excitability was more rapid (106). In patients with lesions of the lower brain stem and upper spinal cord both the recovery cycle and the pattern of distribution were altered (107). The concept of spasticity as based upon the enhancement of monosynaptic reflex excitability is challenged by a lack of correlation of reflex excitability with the degree of spasticity. The suggestion is made that disseminated spinal cord disease and traumatic spinal section result in the disruption of a propriospinal integrative mechanism with an inhibitory or controlling influence on reflex discharge (108). The prolonged depression of monosynaptic reflex excitability following a light tendon tap, and certain outstanding discrepancies between reflex discharges evoked by stretch and discharges evoked by electrical stimulation of low threshold afferents, lead this group to the suspicion that low threshold monosynaptic afferent activity is not the sole cause of the tendon jerk (109). Similar discrepancies between stretch evoked and electrically evoked reflexes are observed by others [Paillard (110)]. It would appear to the reviewer that in neither form of stimulation is the volley

confined solely to excitatory spindle afferents or solely to inhibitory tendon afferents. That both forms of stimulation involve functionally antagonistic afferents is attested to by the observation that reflex activation is followed by a period of inhibition of subsequent reflexes [Wesslau (111)] and of discharges initiated by voluntary control [Wesslau (112)].

Hoffman (113) finds that the conditions for the development of post-tetanic facilitation of human monosynaptic reflexes are restricted and unphysiological and that the degree of change produced is quite limited. The suggestion is made that the threshold of the motor horn cells plays an important part in the determinism of post-tetanic facilitation [Bonnet (114)]. The effects of antidromic stimulation on monosynaptic [Konig (115)] and polysynaptic [Konig (116)] reflexes have been described. Reflex responses resulting from the stimulation of C fibers in the toad (117) and from the stimulation of splanchnic afferents in the dog (118) are described. As an outgrowth of the finding that action potentials of the phrenic nerve are augmented by section of the nerve (119), it is noted that section of ventral roots on the stimulated side of a frog will alter reflex activity of contralateral motor neurons (120). Early and late reflexes evoked by mechanical stimulation have been recorded from the human orbicularis oculi, orbicularis oris, and mentalis (121, 122). These are said to undergo characteristic changes in parkinsonism and amyotrophic lateral sclerosis. Exteroceptive abdominal reflexes, which may be elicited from puppies, disappear at approximately six months of age (123). Brooks & Fuortes (124) note differences between the electrical concomitants of reflex activity discharged into flexor muscles by single weak stimuli and those occurring later and contemporaneously with the development movements of withdrawal. They consider very seriously the possibility that the brief initial discharge is in reality a monosynaptic discharge and that the later afterdischarge associated with movement is the result of the elaboration of the spinal reflex activity brought about through internuncial pathways.

A study of the reflex discharges from motor neuron pools containing chromatolyzed motor neurons contributes further evidence of plasticity and lability in spinal reflex pathways [Downman, Eccles & McIntyre (125)]. The authors speculate upon the possibility that chemical changes in the vicinity of the chromatolyzing neurons produce alterations in the structure and disposition of axon terminations and boutons.

*At the level of the brain stem.*—Spinal reflex excitation of phrenic motor neurons by single somatic afferent volleys is apparently difficult to achieve [Calma (126)], but delayed discharges produced by such volleys may be relayed through the respiratory center. It is indicated that the pneumotaxic center may be localized in the extreme dorsolateral portion of the anterior pontine tegmentum in what might be described as the nucleus dorsalis lemnisci lateralis [Tang (127)]. In a re-examination of the responses which may be elicited by stimulation of the medullary reticular formation it is found that inspiratory and expiratory effects, pressor and depressor effects, and inhibitory and facilitatory effects may be less clearly segregated to distinct

portions of the reticular formation than is commonly believed [Bach (128)]. No evidence was obtained indicating that any two or more of these functions are localized invariably in a common anatomical zone. The suggestion is made [Bach (129)] that facilitatory and inhibitory effects resulting from reticular stimulation may be mediated via a neurohumoral pathway. The chemoreflex emetic mechanism [Wang & Borison (130)] is said not to be involved in veratrum-induced emesis. This form of emesis is dependent upon actions<sup>n</sup> exerted upon the cells of the nodose ganglion [Borison & Fairbanks (131)].

Single unit recordings during rotatory vestibular stimulation lead to the conclusion that the cells of the vestibular nuclei receive only an ipsilateral contribution from the vestibular nerve but that the cells of the reticular formation receive both an ipsilateral and a contralateral contribution from the vestibular nuclei [Gernandt & Thulin (132)]. The notion of a dual central distribution of vestibular impulses is borne out by a study of the influence of vestibular stimulation on spinal cord motoneurons [Gernandt (133)]. The facilitatory effect of spontaneous vestibular impulses on both flexor and extensor monosynaptic reflexes is relayed predominantly over the reticulospinal tract [Gernandt & Thulin (134)]. With both eighth nerves intact, rotatory stimulation produces a reciprocal action on flexor and extensor monosynaptic responses, again over a reticulospinal pathway. Section of one vestibular nerve abolishes the reciprocal nature of the effect (134). Postural alterations in cats following lesions which involve both the vestibular nucleus and reticular formation of one side suggest that the posture of the head as well as that of the extremities is under the influence of the reticular formation [Kemberling, Baird & Spiegel (135)].

*Cerebellum.*—A combined neurohistological and neurophysiological study of the systems afferent to the avian cerebellum has been described by Whitlock (136). The evoked potential technique revealed a somatotopically organized tactile area as well as visual and auditory receiving areas which are closely homologous in their distributions to those described for the mammalian cerebellum (137). A nucleus reticularis paramedianis has been described as a separate entity in the reticular formation of the bulb. It receives descending afferent fibers from the brain stem as well as ascending afferents from the spinal cord, and discharges to the cerebellar cortex of both sides [Brodal (138)]. The afferents in articular nerves [Haddad (139)] and in superficial and deep sensory nerves [Morin & Haddad (140)] are said to project to the cerebellar cortex over a variety of pathways. One is reminded in this instance of the eight possible pathways between the spinal cord and cerebellum which have been defined anatomically by Brodal & Rexed (39).

An important contribution suggesting the possibility of spontaneous discharge from the nucleus fastigius, even in the absence of the cerebellar cortex, has been neglected by previous reviewers of this series [Chambers & Sprague (141)]. A careful study of the effects of faradization of the vermian portion of the anterior lobe has been carried out in an attempt to reveal the mechanisms underlying the apparent reversals which may be obtained

by alterations of experimental conditions [Brihaye (142)]. Reciprocal effects on extensor and flexor reflexes are recorded. It is found that the effects on postural tonus may differ from the effects upon reflex activity. The author considers that the results may best be explained on the basis of a dual cerebellar system relaying through the inhibitory and facilitatory centers of the bulbar reticular formation; variations in the distribution of cerebellar influences are regarded as the result of alterations in the pattern of tactile and proprioceptive activities entering the cerebellum and reticular formation at the time of cerebellar stimulation. Bursts of activity have been recorded from bulbar reticular elements which are accompanied by diminution of decerebrate rigidity [Mollica, Moruzzi & Naquet (143)]. Activity in such units may be augmented by cerebellar discharges accompanying positive polarization of the cerebellar cortex (144). The somatotopic localization of ipsilateral movements produced by localized anterior lobe stimulation in the unanesthetized animal has been described [McDonald (145)]. The development of denervation sensitivity on the part of vestibular neurons is said to follow unilateral ablation of the cerebellar cortex and nuclei [Cook & Stavra-ky (146)]. Seizures subsequent to injection of strychnine into the cerebellum are described and are said to be abolished following destruction of the Purkinje cells [Johnson *et al.* (147)]. Electrical manifestations of convulsive activity in the cerebellum of the unanesthetized cat appear to originate from two sources; low voltage, high frequency discharges originating from the cerebellar cortex itself, and high voltage (10 to 30 per sec.) waves originating from the strychnine convulsions in the spinal cord and imposed upon the cerebellum by virtue of activity in its spinal afferents [Bremer & Bonnet (148)].

Studies of hypothalamic function as manifested by its influence over the endocrine system (149 to 152), temperature regulation (153, 154, 155), control of food intake (156, 157), and cardiovascular adjustments (158 to 161) are regarded as not pertinent to the scope of the present review.

*Influences from the cerebral level.*—An investigation of the results of stimulation of the cerebral motor area with currents of various parameters is unique for its careful and revealing study of method [Lilly, Austin & Chambers (162)]. The cortical sensitivity to variations in frequency and in pulse width is defined for movement thresholds and measured in terms of current and in terms of coulombs. A similar but less extensive study has been made of the responsiveness of the human motor cortex to electrical stimulation (163).

The variability of single motor unit responses to long (5 msec.) pulses applied to the motor cortex, coupled with the lack of any rigid or absolute relation between a cortical point and a responding spinal motor neuron, is regarded as evidence that the neural pathway from the cortex to a ventral horn cell arises from many portions of the motor cortex and not only from its lowest threshold part [Liddell & Phillips (164)]. The fact that variation in the response to corticospinal excitation may be dependent upon influences operating at the spinal cord level has been most emphatically demonstrated by



Landau (165). Movements produced by submaximal tetanic stimulation of the medullary pyramid in the decerebrate cat were seen to produce a variety of responses ranging from steady posture holding to regular phasic walking movements. Those causes for variation which could be defined included stimulus intensity, initial posture, afferent nerve activity, etc. Inhibition, occurring independently of reciprocal contraction, was demonstrated. The author suggests that the pyramidal system merely contributes one element to a complex time-space pattern and that physiological patterns of total neural activity are of more critical importance in the organization of movement than are structural relations alone. The important role of the spinal organization is also demonstrated by the observation that narcotics raise the threshold to pyramidal stimulation of muscles of the hind limbs to a greater degree than that of muscles of the forelimbs [Petersen (166)]. Similarly, distal muscle thresholds were seen to be affected by lower concentrations of anesthetics than those required for an equivalent effect on proximal muscles.

Utilizing chemical stimulation, a masticatory area with an unusual extra-pyramidal discharge path has been described in the dog [Hayashi (167)]. Pyramidal origins have been studied in the dog [Corriol & Maffre (168)] using the antidromic technique described by Woolsey & Chang (169). The responses of single pyramidal fibers to rectangular electrical pulses of various durations have been described (170). Delgado's studies of the buried motor cortex of the cat (171) and of the reactions of waking, freely mobile cats to electrical stimulation of the motor cortex (172) were described in the previous review of this series (40).

The excitability of the motor cortex to electrical stimulation has been tested using as an index the indirect portion of the evoked pyramidal discharge [Wall, Remond & Dobson (173)]. Conditioning the preparation by means of a light flash was found to result in an increase in cortical excitability when measured in this way. The failure of cortical, geniculate, or collicular ablation to diminish this effect may, in the reviewer's opinion, signify that the effect is mediated over the collateral input from the visual system to the reticular activating system. However, when spontaneous discharges are recorded from fibers which are identified with axons of the pyramidal system [Mollica & Rossi (174)] such discharges are found to be abolished during cortical activation elicited by sensory stimulation or by electrical stimulation of the intrathalamic portion of the activating system [Whitlock, Arduini & Moruzzi (175)].

The old observations of Mott & Sherrington (176) are being subjected to a re-evaluation and further analysis. Lassek (177) finds that unilateral dorsal rhizotomy through cervical and upper thoracic levels produces a profound paralysis of the upper limb of the monkey which endures for as long as four months. The potency of the dorsal root system in maintaining normal control of movement seems to center around the seventh cervical dorsal root (178). The deficits produced by dorsal rhizotomy in the kitten are not so profound as in the monkey, and when produced in the infant monkey undergo no restitution with advancing age (179).



In the light of these many long-suspected but newly-defined influences on motor activities, and with increasing awareness of the importance, throughout the central nervous system, of total patterns of activity in time and in space, the reasons for our lack of understanding of the complex mechanisms which underlie even the most simple of motor acts become apparent.

*The limbic lobe and related structures.*—The problems relating to this ancient portion of the cerebrum, so long and so unfruitfully associated with the olfactory system even in microsmatic man, show promise finally to succumbing to the onslaughts of numerous investigators. Future investigations will be facilitated by the anatomical studies of the relationship between the hippocampus, hypothalamus, and temporal lobe [Adey & Meyer (180)], and of the efferent fibers from the hippocampus in the monkey [Simpson (181)]. Taking off from Broca's original definition of the limbic lobe (182), MacLean & Pribram have subjected the area to study by the method of strychnine neuronography in the cat (183) and in the monkey (184). On the basis of reciprocal and unidirectional firing, five regions of cortex around the hilus of the hemisphere and five associated segments of the neopallium may be delimited. The authors hope that such subdivision of the cortex will serve a useful function in guiding future experimental analyses.

The stimulation, in unanesthetized man, of numerous points distributed over the anterior end of the hippocampal gyrus, the ventral and medial surfaces of the temporal pole, the anterior portion of the insula, and the anterior limbic gyrus are reported to produce respiratory inhibition accompanied by alterations of consciousness, muscular tonus, and autonomic activities. Depression of the electrocorticogram was an occasional finding [Kaada & Jasper (185)]. In studies of experimental animals, two interpretations have been made as a result of the stimulation of the more anterior portions of the limbic system through chronically implanted electrodes in unanesthetized freely mobile animals. Some reactions are interpreted as manifestations of emotion which in man has a disagreeable aspect [Gastaut *et al.* (186)]. This interpretation has been challenged on the basis of a study of the afferent systems which project to the same areas [Dell *et al.* (187)]. Dell and his co-workers conclude that these portions of the brain are the receiving zones for gustatory and visceral as well as olfactory sensibilities. Thus it is suggested that the reactions seen by Gastaut and his collaborators (186) represent motor reactions to sensation rather than the integration of emotional behavior patterns. Hess, Akert & McDonald (188) interpret the cyclic highly organized forms of movement (licking, snapping, retching), which developed in their animals during the stimulation of the orbital gyrus, on the basis of its function as a receiving area for exteroceptive and interoceptive sensation. MacLean & Delgado (189) have reported similar and more complex behavioral responses to stimulation of the frontotemporal portion of the limbic system. These authors conclude that "this portion of the brain is concerned with the organization of the oral activities of the animal as they pertain to feeding and to the vocalization, attack and defense

involved in obtaining food." Gastaut (190) suggests that the rhinencephalon is distinguished by two different systems; one concerned with the acquisition and utilization of food, the second, concerned with the elaboration of emotional behavior.

Among the many autonomic responses which have been recorded as a result of stimulation of the limbic lobe, there must now be included observations of accentuation and inhibition of the gastric motility (191). Bilateral lesions of the medial and lateral portions of the amygdaloid complex in rats and cats produced no alterations in food intake and no rage reactions (192). Bilateral lesions of the anterior cingulate gyri in a single human were accompanied by apathy, akinesia, mutism, indifference to pain, and progressively deepening stupor (193). The alterations produced in a group of psychotics by undercutting and isolating the anterior cingulate cortex are briefly described [Livingston (194)]. Alumina cream injected into the amygdaloid nucleus of cats has produced paroxysmal behavior disorders resembling those produced by electrical stimulation (195).

#### THALAMOCORTICAL RELATIONS; THE AROUSAL REACTION, RECRUITING RESPONSES, CONSCIOUSNESS

*The brain stem activating system.*—An activating system in the brain stem, comparable to that in the cat (196), has been described in the monkey [French, Von Amerongen & Magoun (197)]. As in the cat (59), the afferents to the system are found to be derived from a variety of sensory systems; rapidly repeated stimuli produce desynchronization; occlusive interaction occurs between stimuli from various sources. Reasoning from the behavioral changes which are associated with electrocortical desynchronization, the authors suggest that activity in this system is responsible for the maintenance of awareness and alertness. Similar cortical desynchronization is also produced by repetitive stimulation of portions of the thalamus of the guinea pig [Green & Morin (198)].

In addition to auditory, visual, and somasthetic inputs to the activation system it is now found that a very potent source of activation may be derived from the olfactory receptors [Arduini & Moruzzi (199)] and by stimulation of vagal afferents [Zanchetti, Wang & Moruzzi (200)]. An attempt has been made by Gellhorn and his colleagues (201, 202) to assay the relative abilities of the various sensory systems to produce hypothalamic and cortical desynchronization and behavioral arousal. Nociceptive stimulation, combined tactile and proprioceptive stimulation, auditory stimulation, and visual stimulation are found to be decreasingly effective. Gellhorn's studies lead him to a dual concept of sensory perception according to which perception depends upon the interaction in the sensory projection area of activities projected over the direct lemniscal pathway and the indirect activating system.

Whitlock, Arduini & Moruzzi (203) find that high frequency unit discharges during the spikes induced by liminal strychninization were abolished by natural or electrical excitation of the activating system, thus recalling

Berger's original interpretation of alpha blockade as an inhibition. A more extended investigation in the rabbit also revealed that a reversal from diminution to augmentation of spiking could be produced by subjecting the animal to additional intense afferent inputs [Lairy-Bounes, Parma & Zanchetti (204)]. The more prominent occurrence of diminution in the rabbit and the more prominent occurrence of augmentation in the cat [Arduini & Lairy-Bounes (205)] is ascribed to differences in the background level of cortical excitability in the tranquil unanesthetized, unrestrained rabbit as compared to the "encephale isolé" cat. Variations in the influence of the activating system upon various forms of human electroencephalographic abnormality are also ascribed to variations in the cortical excitatory state existing at the time of the stimulation [Li, Jasper & Henderson (206)].

To date the studies of the relationship between electrical activation of the cortex and behavioral arousal have emphasized almost exclusively the cortical responses to reticular activation. Bremer and his colleagues now call attention to the role played by the cerebral cortex itself in this relation. It is reported that stimulation of certain areas in the cerebral cortex produces responses in the reticular formation which are indistinguishable from those produced by sensory stimulation (207). Interaction between corticofugal impulses and impulses in the reticular activating system indicates convergence. Brief electrical excitation of one hemisphere provokes electrical activation of the entire dorsolateral cortex bilaterally and of the reticular formation independently of the corpus callosum (208). Cortical activation induced by auditory stimulation may be abolished by bilateral thermal coagulation of auditory I and II even though activation may still be produced by other forms of sensory stimulation (209). The authors conclude that

the cerebral cortex utilizes the central gray matter for elevating the activity of its own neuronal network. At the same time the reticular formation concentrates and amplifies all of the nervous influences which lead to awakening, not only those from the sensory pathways but also those from the cortical areas.

Although the corpus callosum is not essential to cortically-induced activation, a study of the interaction between callosal and auditory volleys indicates a facilitatory effect of a callosal upon a subsequent auditory response (210). Callosal facilitation could be eliminated by barbital narcosis, section of the corpus callosum, and by movement of the pickup electrode (211). Furthermore, during the course of spontaneous cortical activation, local paralysis of one auditory cortex with potassium chloride reduced the amplitude of a click response on the opposite side. Thus, the author concludes that during cortical activation the callosal fibers transmit facilitatory influences between the two sides.

*The recruiting response.*—Since the early description of the recruiting response by Dempsey & Morison (212) and its relationship to the diffuse thalamic projection system as indicated by Jasper (213), a great deal of time and effort has gone into a precise definition of the response, the system, and its distribution. The functional significance of the system, however, still

evades precise definition. The anatomical relationships of the thalamic reticular nucleus which were described by Rose (214) for the cat and rabbit are found to hold true also for the monkey [Chow (215)]. Responses suggestive of the existence of a diffuse thalamic system have been recorded from the forebrains of the guinea pig (198) and the frog (216).

Starzl & Whitlock (217) indicate that the origins of the system in the monkey include the centrum medianum, the intralaminar nuclei, the inferior part of the medial nucleus, centralis anterior, and the anterior portion of the reticular nucleus. These nuclei appeared to be mutually interconnected and to discharge via intrathalamic connections into the medial and anterior nuclei, lateralis complex and pulvinar. Recruiting responses were recorded only from the association cortex with the great preponderance of the effects passing into the frontal areas. An attempt has been made to analyze the nature of the recruiting response in terms of its constituent neurons [Verzeano, Lindsley & Magoun (218)]. The authors conclude that the recruiting phases of the complex response are strictly local in their origins, cortical, when recorded from the cortex, and thalamic when recorded from the thalamus. On the other hand, Hanbery & Jasper (219) find that recruiting responses can be recorded from the primary sensory receiving areas of deeply anesthetized cats and suggest that the failure to do so may have been dependent upon light anesthesia and a blockade of the recruiting response by pre-existing cortical activation. These investigators also find that destruction of any one of the specific thalamic projection nuclei does not prevent the development of the recruiting response in the area of projection of that nucleus. It would thus appear that recruiting responses may be initiated independently in the thalamus and conducted to the cortex over a pathway which does not involve the thalamic association nuclei. The recording of recruiting responses from a primary sensory area is confirmed (220). It has also been possible, by thalamic stimulation, to induce recruiting responses in the olfactory bulb (221). Cortical recruiting waves are accompanied by grouped discharges in pyramidal fibers (222).

*Consciousness.*—The relationship between the diencephalon and consciousness and its important function in the control of sleep and wakefulness is commonly accepted. While the discovery of the diffuse thalamic projection system and the reticular activating system gave impetus to further studies in this area, the definitive solution to the problems remains to be achieved. Sleep may or may not have been produced by electrical stimulation of the head of the caudate nucleus in man (223). The discussion which followed the presentation of this paper emphasizes the semantic difficulties and the need for more careful utilization of precise terms.

A valuable contribution has been made in the form of a description of the cortical and subcortical electrical changes occurring in natural sleep in the cat (224). Hess' (225) observation of sleep production by diencephalic stimulation was reconfirmed. Characteristic sleep patterns are said to occur first in subcortical structures and only later at the cortical surface (226).

Abnormal unconsciousness has been produced in monkeys [French &

Magoun (227)] and in man [French (228); Jefferson (229)] by lesions which involve the upper end of the reticular activating system. An akinetic and apathetic state may also be produced by lesions of portions of the diffuse thalamic projection system and the basal diencephalon [Meyer & Hunter (230)]. A wider variety of behavioral changes ranging from increased irritability and rage through lethargy, somnolence, and reduced reactivity to obnoxious stimuli is produced by a variety of thalamic injuries [Schreiner *et al.* (231)]. Notes of caution against the uncritical use of terms, and against an eagerness to associate a functional attribute with a single anatomical area are offered [Cloake (232); Cairns (233)]. Thus, while the maintenance of cortical excitability and the integration of the many and continuous sensory influences with the background of cortical activities [Williams (234)] would appear to be functional attributes of the activating system and the diffuse projection system, the manner in which these systems carry out these functions remains to be elucidated.

#### INTRACORTICAL RELATIONSHIPS

Microelectrode techniques show promise of leading to the answers to some of the more perplexing problems of intracortical physiology. Such techniques have been applied to the primary cortical receiving areas [Amassian & Thomas (235)], to the visual cortex [Baumgarten & Jung (236)], and to a study of the action of drugs and asphyxia on cortical cells (Thomas & Jenkner (237)). Older observations concerning the dissociation between wave activity and unit discharge in the cerebral cortex (238) and cerebellar cortex (239) have been confirmed [Li, Jasper & McLennan (240, 241); Burns (242)]. Intracellular cortical leads suggest that membrane potentials and slow voltage fluctuations recorded extracellularly may be related (Albe-Fessard & Buser (243)).

Problems relating to intracortical excitation, inhibition, and transmission have been subjected to continued attack. The interactions between evoked and spontaneous activity (244) and the alterations of excitability following an evoked response in the visual cortex (245) have been studied by Bishop & Clare. Cortical responses to direct stimulation of an isolated slab [Burns & Grafstein (246)] and of different levels in the depth of the cortex [Bishop & Clare (247)] have led to suggestions concerning the manner of function of different anatomical elements of the cortex. The cortical response to activation of callosal afferents has been analyzed in terms of the cortical elements contributing to the response [Chang (248)], and the interactions between callosal responses and responses evoked by direct stimulation and activation of thalamic afferents has been studied [Chang (249)]. The cortical electrical activity at various depths during the transition from normal to convulsoid behavior is described [King, Schricker & O'Leary (250)].

The phenomenon of "suppression" continues to be attacked [Druckman (251); Sloan & Kaada (252)]. Vascular alterations during spreading depression were subjected to analysis by Van Harreveld & Stamm (253). It is argued that the slow potential change accompanying spreading depression

does not have its origin in an asphyxial depolarization of cortical neurons (254). Pentobarbital and ether are found to have different effects upon the slow potential changes accompanying spreading depression (255).

An unusual hypothesis has been advanced to account for the slow waves of electrical change in the central nervous system (256). The resistance of the anesthetized cerebral cortex to ischemia has been measured (257). Studies have been made of the development of electrical activity in the cortex of the immature albino rat (258) and its relation to hibernation in the woodchuck (259).

#### PHARMACOLOGY

Several studies of this group are of particular importance since they deal with substances which are in extensive use as tools in neurophysiological investigation. Scherrer (260), studying the actions of strychnine, finds that it has both a depressant and a threshold lowering effect. Brooks & Fuortes (261) find evidence that strychnine produces a degree of steady depolarization in spinal cord neurons which is the cause of the repetitive discharge of impulses. As the result of a study of disynaptic and polysynaptic reflex interactions, Bradley & Eccles (262) suggest that the increase in polysynaptic excitatory actions produced by strychnine is the result of a depression of inhibitory processes acting on interneurons. According to Chang's observations on cortical actions (263), strychnine produces its effects through a depressive action on presynaptic fibers or receptive membranes and by improving the efficiency of synchronization of nerve impulses.

Natural and synthetic curare-like agents were found to produce no alteration in the electrocortical reactions of the unanesthetized rabbit [Bovet & Longo (264)]. In contrast to these findings, Chang (263) has found that *d*-tubocurarine and natural curare have a strychnine-like effect upon the anesthetized cerebral cortex when topically administered in very low doses and when administered via the intracisternal route. Administration via the intravenous route also produced spontaneous cortical discharges but only at higher concentrations. In every respect, Chang finds that the actions of strychnine and curare are identical.

In a precisely described and clearly presented group of experiments, Austin & Pask (265) find that the depressant influence of ether is exerted almost entirely upon the ventral horn cell rather than on the synaptic conduction pathways between the dorsal roots and ventral horn.

#### TECHNIQUES

A preliminary note concerning an "isolation technique" to be used in the study of cortical projection systems has appeared [Levin, Von Bonin & Crandall (266)]. Carpenter & Whittier (267) have performed a valuable service by compiling a detailed historical review and experimental study of the stereotaxic technique and the technique of production of lesions in the central nervous system. A technique for relating muscular tension to electromyographic recordings in the human is described (268). Brazier & Casby

(269) describe the initial steps in the application of cross correlation and auto-correlation techniques to problems concerned with the detection of rhythmic events in an arrhythmic background and to the differentiation between signal and noise in the electroencephalogram. An electromagnetically controlled signal marking pen for use on electroencephalographic equipment is described (270). Modifications of Weale's technique for the production of glass capillary microelectrodes are said to result in improvements in ease of production and in performance (271, 272). Dowben & Rose (273) have published their technique for the manufacture of glass microelectrodes filled with gallium or indium alloys.

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## VISCERAL FUNCTIONS OF THE NERVOUS SYSTEM<sup>1,2</sup>

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Of the numerous important contributions to the subject special mention might be made of the new information gathered on the central representation of a number of visceral functions and the new approaches to the understanding of the interrelations between psychic activity on a wider basis and the visceral functions. Also the mechanisms by which mental disorders and various kinds of stress situations influence the automatically regulated processes constitute an important lead in a comparatively new line of research.

### CEREBRAL CORTEX

In a thought-provoking article Hess (106) discusses the relations between experimental physiology and psychology and points at the fact that certain affective responses produce effects comparable with specific emotional patterns. He concludes that such phenomena can only be explained by assuming a cortical action in conjunction with lower levels of the central nervous system since such reactions can be elicited from circumscribed areas in the thalamus and hypothalamus. Thus subcortical processes must be linked up with consciousness. From the standpoint of psychiatry these concepts are obviously of high significance and should form a profitable basis for further psychiatric research, the urgent need of which has been stressed (129).

The interrelation between the cortex and the brain stem in behaviour has also been the subject of an interesting article by Ingram (116). He reported that relatively small lesions in the ventromedial hypothalamic nuclei caused an extreme, chronic, and incurable savageness in cats, suggesting that these areas serve as an inhibitory center for the rage impulses originating in other areas. Since the activity is well directed and discriminating the malevolent attitude of savage cats apparently involves some cortical mechanisms which probably are operating also after destruction of the ventromedial hypothalamic area.

The effect of psychoanalysis on gastric ulcer has been studied by Stine & Ivy (189), who stress the importance of similar studies. Using a method for the production of a potentiated response to psychic stimulation Burstall & Schofield (30) found that all of the test dogs showed an increase of both acid and pepsin output in the Heidenhain gastric pouch, while three of five animals did not respond to insulin hypoglycemia. Vagal release of gastrin from

<sup>1</sup> The survey of literature pertaining to this review was completed in June, 1953

<sup>2</sup> The following abbreviations have been used in this chapter: cr (conditional reflex); EEG (electroencephalogram); STH (somatotropin); TEPP (tetraethylpyrophosphate); TEA (tetraethylammonium); ACH (acetylcholine); ECG (electrocardiogram); DOPA (3,4-dihydroxyphenylamine).



the main stomach was considered as responsible for the effect. In a subject with gastrotomy a pectin meal caused no cephalic secretion of gastric juice which was obtained by a meal chosen voluntarily (142).

Gantt & Dykman (79) have made an extensive study of the development of tachycardia as a conditional reflex in dogs. The effect was produced by (a) painful stimuli, (b) psychic stress (conflicting stimuli), and (c) other factors involving especially "interpersonal relations." The tachycardia was accompanied by few or many other symptoms of increased activity of the autonomic system, such as gastric hypersecretion, vomiting, diarrhoea, altered activity and blood sugar tolerance, and symptoms in the sexual sphere. These symptoms continued throughout the life of the dog. The cardiac conditional reflex lasted longer than other more specific crs,<sup>2</sup> indicating the persistence of the emotional background. Even after intervals of months and years the symptom pattern could be reestablished without induction periods. The cardiac component of the cr was often difficult to extinguish, and the crs often formed the basis for an autogenic development of a psychopathological (neurotic) condition. Observations in man (130) support the hypothesis that individuals tend to respond with a typical pattern of autonomic activation, irrespective of the stress-provoking factor. Emotional stimuli as well as thermal stimuli elicit sweat response from the forehead (143).

Alvarez-Buylla & Russek (4) observed that certain vegetative responses elicited by tactile stimuli in the dog could be simulated by the injection of cyanide. The responses of electrical and chemical stimulation of the fronto-temporal portion of the limbic system seemed to indicate that this part of the brain is engaged in feeding and other reactions such as attack and defense, associated with obtaining of food (144).

Funkenstein, Greenblatt & Solomon (75) continued studies on a test of the autonomic nervous system [intravenous epinephrine and methacholine (Mecholyl)] and found it of prognostic significance in relation to electroshock treatment. The data obtained showed significant differences between the means of the test responses in the "improved" and "unimproved." Patients showing a "favourable" response to these tests concerning electroshock treatment also showed a higher rate of improvement with ether intravenously than did patients whose test would indicate a poor prognosis with electroshock (76). The effect with ether was less satisfactory in the favourable cases than that which would be expected with electroshock. No correlation with clinical improvement from electroshock was found by Altschule, Parkhurst & Owens (3), when the glucose tolerance test was used as an index in 12 psychotic patients.

According to Alexander & Neander (2) those cases of psychic disorder which did not respond to electric shock or insulin therapy with either eosinopenia or eosinophilia show a poor prognosis for such treatment. Endogenous eosinopenia has been observed in mentally deficient patients of both sexes (98). The interesting observation was made that this finding was correlated

with the initiation of daily activities which makes it important to time the blood sampling accordingly. Signs of both hyperadrenalinism and hypo-adrenalinism in schizophrenic men were obtained by Hoagland *et al.* (108). Electroshocks known to affect behaviour in the rat produced hypertrophy of the adrenal glands, presumably as a result of pituitary stimulation. Anesthesia prevented these changes (171).

Increased autonomic nerve activity after experimental concussion in dogs consisting of increased blood pressure and carotid blood flow, respiratory arrest, and cardiac arrhythmia has been reported (25). The cardiovascular reaction pattern is similar in electroshock. It is pointed out that loss of consciousness associated with clinical concussion may occur without diminished cerebral blood flow.

The effects of epinephrine and norepinephrine in doses of 1 to 10  $\mu\text{g./kg.}$  on the EEG<sup>2</sup> during and after electroshock were studied by Minz & Domino (150) who observed prolonged afterdischarge and shortened cortical extinction by these ergones and by amphetamine, while acetylcholine and histamine depressed the response. The effect of epinephrine was concluded to be a direct action on the central nervous system.

Striking effects of epinephrine and norepinephrine on the transmission processes in the spinal cord have been described by Skoglund (185). The reflex vasodilatation after intravenous epinephrine might be due to central inhibition [Gruhzit & Moe (96)]. It was also noticed that norepinephrine was less active.

Kaada & Jasper (121) found respiratory inhibition in man after electrical stimulation of the temporal lobe, the hippocampal and limbic gyri, and the insula. A feeling of tiredness and sleepiness accompanied these effects. A rise of blood pressure in the cat was observed by Kell & Hoff (122) after stimulation of the anterior sigmoid gyri or by stimulating the brain with a pair of frontally placed percutaneous electrodes. The descending pressor pathway from the frontal lobe runs bilaterally in the spinal cord and coincides with the descending spinal vasomotor pathway in man. The sympathetic vasodilator system has a representation in the motor cortex (57).

#### HYPOTHALAMUS

Electrical rhythms of the hypothalamus independent of the cortex were recorded by Green & Morin (93) who also found slow rhythm in the anterior and fast in the posterior hypothalamus. The electrical activity was only slightly influenced by anaesthetics, drugs, and physiological stimuli. When hypothalamus was injured, simultaneous high voltage bursts appeared in the hypothalamus and the cortex. Sine-wave stimulation of the hypothalamus caused arousal or activation-type responses and seizure-type responses. Application of single shocks from various hypothalamic areas caused diffuse responses from the cerebral cortex and cerebellum, while changes of convulsive character were induced by repetitive stimulation.

The mechanisms underlying the 24-hr. periodicities have been discussed

by Halberg (97) on the basis of adrenal and other activities. He finds that the temporal placement of the eosinophilic and the mitotic rhythm might be controlled by the ACTH and STH<sup>2</sup> production. Deviations should be measured from the cyclic levels and not from a "base-line." A further contribution to this problem has been presented by Mills & Stanbury (149) who found in five subjects placed on a 12-hr. cycle of activity (meals, illumination, etc.) that the renal excretory rhythm still retained its 24-hr. periodicity. However, during the sleeping hours the urine became alkaline, and some other changes due to activity (phosphate excretion) occurred in a 12 hr.-cycle.

A number of authors have made studies of the effect of stress on autonomically innervated organs and functions. Some of these have already been referred to. Funkenstein (74) finds that methacholine, which precipitates asthma in asthmatic patients, does not have this effect during stressful situations. The interesting observation was made during cardioballistographic studies during stress that on some occasions a norepinephrine-like pattern of response was obtained and in others an epinephrine-like. It was concluded that the failure of methacholine to produce asthma during stress was due to liberation of catechol amines. This conclusion is supported by findings (63) in which it was shown that psychic and physical stress is regularly accompanied by an increased output of norepinephrine or epinephrine or both in urine, indicating an increased release in the body. Many observations of visceral disturbances in stress may be partly explained on these lines as can also the partial blockade of the stress symptoms by sympatholytics, acting either centrally or peripherally (174). If the increased hypothalamic activity in stress also involves stimulation of sympathetic cholinergic vasodilators it is understandable that peripheral blocking with atropine can also offer some protection, as shown by the blood pressure of adrenalectomized dogs (86). The hypertensive patient reacts to stressful situations with a greater tendency to vasoconstrictor reactions than does the normal subject (188).

Eosinopenia is regarded as one of the foremost signs of stress, and its occurrence after epinephrine administration for a time led to the conclusion that this was due to a release of ACTH. Anterior lesions of the hypothalamus did not prevent the response to epinephrine, formalin, and histamine in the cat, but after posterior lesions the eosinopenic effect disappeared. When tuberal and mammillary areas were electrically stimulated eosinopenia ensued (166). Surgical stress appeared to be the reason for the increase in 17-ketosteroid excretion and eosinopenia after complete buffer nerve section (15).

It has been concluded (141) that excitation of adenohypophysis can occur independently of humoral or neurogenic influences from the hypothalamus, judged by eosinopenia appearing after major surgical operations in dogs after hypophysial stalk section and ablation of the adjacent ventral half of the hypothalamus. Similarly Thomson & Zuckerman (192) reported that the gonads of the ferret were activated by light under such condition

that retinal impulses apparently could not be transmitted via the hypothalamus to the pars distalis of the pituitary either by nervous or neurohumoral pathways.

Visceral effects of anaesthesia may occur under various conditions (24). After total sympathectomy in the dog ether failed to produce metabolic acidosis and hyperglycemia which is interpreted as resulting from a blocked output of epinephrine. The renal vasodilatation caused by inhaled ether after renal denervation (148) may be explained along the same lines. The increase in heart rate and contractile force observed (170) during high spinal anaesthesia with procaine is interpreted as cerebral excitation and discharge of epinephrine caused by rapid passage of procaine into the blood stream. Uvnäs and co-workers have continued their studies on the sympathetic-cholinergic vasodilator system and have shown that this extends to the motor cortex. By stimulation in a "vasodilator area" in the supraoptic part of the hypothalamus the vasodilator fibres to the muscles may be selectively activated (57). It is suggested that the primary vasodilation during muscular exercise depends on activation of this system.

Stimulation of the amygdaloid nuclei produced a temperature rise and responses from the gastrointestinal tract and respiration, pointing to a close connection between this complex and visceral functions (125, 126). Electrolytic lesions of the amygdaloid nuclei in rats caused no change in food intake but a decrease in spontaneous activity and a fall of body temperature for about a week (6). Also savage rats became more tame. Similar symptoms were observed in the cat. The food intake remained normal in those animals where the lesions did not spread into the lateral hypothalamus. The anorexia caused by amphetamine was diminished or absent in frontally lobectomized dogs (139). In mice rendered hyperactive by *d*-desoxyephedrine hydrochloride (Pervitin), sympatholytic agents decreased the central stimulation while parasympatholytic substances increased it, suggesting an interrelationship between central activity and drugs with actions on the autonomic system (193). A sharply localized feeding center was demonstrated by Delgado & Anand (42), who observed a large increase in food intake in cats after electrical stimulation of the lateral hypothalamus. This effect was apparently independent of the glycemic level.

Further support for a postulated central mechanism of blood glucose regulation was obtained by Dunér (53) who found that hyperglycemia, even when restricted to the head of the animal by cross-perfusion, lowered selectively the epinephrine output of the suprarenal gland in the cat. Suggestive evidence of the same reaction was found after local injections of glucose in the hypothalamus. Using  $C^{14}$ -glucose Searle & Chaikoff (180) observed that the transfer of glucose from liver to the blood ceased upon introduction of a massive dose of glucose into the blood stream.

Vasomotor changes leading to fatal hemorrhagic edema in the lungs of rats were observed after electrolytic lesions of the rostral hypothalamus by Gamble & Patton (78). The authors suggest that such lesions interrupt

descending pathways from the critical preoptic region. Unilateral lesions were ineffective. Several visceral symptoms from the cardiovascular apparatus were observed as a result of immersion of subjects in warm or cold water (44).

The histological relationship between the hypothalamus and the peripheral autonomic nervous system has been studied after unilateral removal of cervical sympathetic ganglia of newborn and young animals (159). Marked homolateral degeneration signs in the periventricular fiber system in hypothalamus and in the midbrain were reported. After vagus section hypothalamic degeneration signs were also noted.

The problem of neurosecretion from the diencephalon has been studied with histochemical methods in teleosts and mammals (176). Substances showing positive reactions to periodic acid schiff, Millon's test, and Sudan black had the same localisation as the gomori substances, suggesting that the "neurosecretion" is a glucoprotein complex. Rothballer (172) described mobilization of neurosecretory material and vasodilatation following painful stimuli, and Dawson (41) found histological evidence for the termination of neurosecretory fibers within the pars intermedia in the frog. Scharer (175) advanced the hypothesis that the neurosecretion formed in the insect brain is transported via the *nervi corporis cardiaci* to the corpus cardiacum and stored there. The intercerebralis-cardiacum complex is regarded as an analogon to the organ-x-sinus gland system in crustaceans and the hypothalamo-pituitary system of vertebrates. The peculiar nerve cells described in the adenohypophysis of *Cyprinus amarus* (146) were considered as a functional link between this organ and the nervous system.

Extracts of hypothalamus have been repeatedly tested for the presence of active principles. Pernow (165), confirming the presence of substance P in the central nervous system, made the interesting finding that it occurs in the largest amounts in the hypothalamus of mammals. Since this polypeptide is biologically highly active the observation may be of high significance. Harris & Holton (102) found vasodilator action in extracts of brain with the highest activity in extracts of nucleus cuneatus and caudatus. Hypothalamic extracts (104) caused leucopenia in albino rats, an effect which might be correlated with the demonstration of considerable quantities of norepinephrine in the hypothalamus (207).

#### BRAIN STEM

Wang & Borison (196) have presented a review of the recently discovered chemoreceptive center ("trigger zone") for vomiting, including the mechanism of action of apomorphine, copper sulfate and cardiac glucosides. Hoff, Breckenridge & Spencer (109) found evidence of a disturbance in autonomic equilibrium in decerebrate dogs, expressing itself in bradycardia, sialorrhea, gastric hypermotility, and hypersecretion, thus producing a syndrome of parasympathetic preponderance.

*Respiratory control and reflexes.*—Tang (191) observed apneustic breath-

ing in vagotomized cats after transection of the brain, caudal to the inferior colliculus. Gasping ensued after secondary transection below the striae acusticae. The findings are taken to show that the rhythmicity of the bulbar respiratory centers are not wholly dependent on afferent impulses from the vagal and pneumotaxic systems. From the effects of isthmus lesions it is concluded that the pneumotaxic center is located in the extreme dorsolateral portion of the anterior pontine tegmentum.

The oxygen concentration of the cerebrospinal fluid within physiopathological limits did not appear to influence the respiratory and vasomotor centers (18). Daly, Lambertsen & Schweitzer (39) obtained evidence for an effect of blood carbon dioxide in maintaining the vagal bronchomotor tone.

The influence of autopharmacologic and other drugs has been studied in a number of investigations. Thus Whelan & Young (201) found respiratory stimulation in man after moderate doses of epinephrine and norepinephrine, independently of the increase of metabolic rate. TEPP<sup>2</sup> produced failure of the respiratory centre (47), while 3-hydroxy-*N*-methylnorphinan (*dl*-Dromoran) caused effects on the respiration similar to those appearing after decortication or midcollicular decerebration (23). The authors discuss their results in the light of the neural control of respiration by the reticular system of the brain stem. According to Enders & Schmidt (58) papaverine stimulates the respiratory center directly. This may even be the case with serotonin, although the respiratory stimulation includes effects via the vagus and sinus nerves (48).

The susceptibility of the respiratory center to the surrounding ionic milieu has been studied by Åström (8) and Winterstein & Gökhan (205). Åström concludes from his experiments that the stimulating action of CO<sub>2</sub> on the respiratory center is reduced at low pO<sub>2</sub>, while the hypoxic stimulation via the chemoreceptors is diminished at high arterial cH. The increase in the blood cH after ammonium chloride in the dog causes only a moderate increase in respiration, which is explained by a concomitant fall in central cH (205). Under these conditions the peripheral chemoreceptors only would be stimulated, and the respiratory effect is reversed after their exclusion. The marked difference in cH in the centers and in the blood is explained by the rapid diffusion of ammonia through the blood-liquor barrier. The summation of glomerogenic and liquorogenic stimuli determines the ventilation according to Winterstein's new theory.

Evidence has been presented by C. v. Euler & Söderberg (60) for the presence of chemosensitive receptors in the medulla. In response to carbon dioxide, rhythmical as well as continuous discharges were recorded from the interior of the respiratory centers of the completely denervated rhombencephalon of the cat. The chemosensitive receptors are considered to be responsible for the centrogenic stimulation of respiration. The chemopotentials were specific for the known sites of the medullary respiratory center (61).

No correlation was found by Bach (9) between the somatic reticular facilitatory and inhibitory formations and respiratory enhancement or



inhibition. However, apnea occurred in close temporal correlation with knee-jerk inhibition. Hukuhara *et al.* offer a theory of the mechanism of the nervous regulation of the respiratory movements (114), based on the hypothesis of summation and inhibition of the central activity in the initial and late stages of inflation.

*Cardiovascular control and reflexes.*—The mechanism of the arterial pressure fall in the rat and the cat by morphine was studied by Evans, Nasmyth & Stewart (68). In the cat the effect is chiefly on the vasomotor center but is also due to peripheral histamine release, although this is partly counteracted by a large increase in adrenal medullary secretion. On the rat the effect of morphine was abolished by cutting the vagi. The central depressant action of hydrogenated ergot alkaloids on vasomotor reflexes was confirmed by Winsor (204). Dawes, Mott & Widdicombe (40) concluded that at least three types of physicochemical receptors must be present in the chemosensory units of the carotid and aortic bodies in the dog. A new baroreflex area in the cat situated in the wall of the common carotid artery near the superior thyroid artery is reported by Green (92). Floyd & Neil (72) found that stimulation of the sympathetic nerves to the carotid body increased the "impulse traffic" from the chemoceptors, while baroreceptor impulse activity was not influenced as a rule. The type of stimulus for the baroreceptors is of importance as shown by Ead, Green & Neil (55), who found that pulsatile flow caused greater reflex effects than steady flow at the same mean pressure. It thus appears that the peak thrust during pulsatile pressure outweighs the period of lower pressure. Veratrine had a sensitizing action on the sinus baroreceptors but did not produce a stimulation of its own according to Witzleb (206).

The effectiveness of the pressoreceptor reflexes to moderate hypertension in the presence of pharmacologic doses of epinephrine is not great according to Boxill & Brown (22).

Further experiments on the stimulation mechanism of the carotid body have been reported. Douglas (46) found hexamethonium effective in blocking the carotid responses to nicotine-like drugs but not to anoxia and cyanide. He concludes that the impulses therefore cannot be transmitted through a synapse in the afferent path, similar to those in the autonomic nervous system. Landgren, Liljestrand & Zotterman (131) showed that drugs with anticholinesterase action increased the activity of the chemoreceptors in oxygen want. They also demonstrated that decamethonium was more active in depressing the lobeline action than that of oxygen want. The authors suggest that acetylcholine plays a role as a transmitter of impulses in the carotid body. Vascular reflex actions from various receptor areas have been studied by a number of authors. Weissel *et al.* (199) found a rise in both the pulmonary and systemic blood pressure after carotid occlusion in unanaesthetized dogs but only a systemic rise in anaesthetized animals. Depressor nerve stimulation caused no change in hepatic vessels in dogs under urethane, according to Semba & Kishi (181). Anoxic slowing of the heart in the foetal guinea-pig was ascribed to stimulation of some foetal chemoceptor (94).



Schroeder & Brehm (179) conclude from experiments on unanesthetized dogs that the filling-speed and not the pressure of the atrium is the adequate stimulus for the Bainbridge reflex. According to Leimdorfer (133) respiratory arrest at the end of a maximal inspiration elicits a depressor reflex in man.

Ligation of a coronary artery branch caused a significant degree of vasoconstriction but never vasodilation in anaesthetized dogs [Levy & Frankel (135)], measured in a hind leg. During exercise in the heat, renal plasma flow was reduced more than in cool environment and still more in dehydrated subjects. Filtration fraction went up in all experiments (187).

Gaskell & Burton (82) describe a reflex which apparently is of high significance. Distension of the walls of the veins in a vascular region leads to a decrease in flow which is either attributable to venous constriction (by a myogenic reflex) or, more likely, to arteriolar vasoconstriction. The postulated reflex is not prevented by sympathectomy. The local venivasomotor reflex is regarded as a supplement to the central buffer reflexes in controlling the blood flow in changes of posture of individual limbs of the body.

The effects of the reflex system originating from the receptor area in the sinus and aortic region are not confined to circulation and respiration. Thus Beznák & Liljestrand (19) found that clamping of the carotids caused a considerable decrease in the lymph flow in the left thoracic duct in the cat. Urine flow on the other hand increased.

#### SPINAL CORD AND PERIPHERAL VISCERAL AFFERENTS

For the elucidation of factors involved in nervous transmission processes it is obviously of importance to have a method for the local administration of certain chemicals. Such a method applicable to the spinal cord has been described by Feldberg, Gray & Perry (70).

A study on the vascular pain fibres in the thorax wall has been undertaken by van Harreveld & Lindsley (100). Stimulation of these fibres caused motor reactions and a rise in arterial pressure. The response could not be abolished by removal of the sympathetic chain, in this respect resembling the venivasomotor reflex described by Burton and his co-workers. Using the method of remaining sensitivity van Harreveld & Smith (101) found a loss of pain sensitivity in a small area localized on the cranioventral border of the dermatome after sympathectomy in dermatomes T 10 to L 3. These results apparently demonstrate that afferent fibres for the skin or skin vessels traverse the sympathetic trunk.

Afferent impulses in somatic nerves have been stimulated in the rabbit in experiments by de Molina, Achard & Wyss (152) and responses of circulatory and respiratory functions recorded. A-fibres were concerned with a fall in arterial pressure and an initial inspiratory reaction. Slower fibres of the  $\alpha$ -type were linked with pressor responses and hyperpnea. These reactions may be associated with the discharge of suprarenal epinephrine observed by Euler & Folkow (65) after sciatic or brachial plexus stimulation in the cat.

Introduction of cold air in the trachea of piglets caused shivering mediated by the vagus as afferent path (36). Afferent impulses acting on respira-

tion have been elicited from the intestine by occlusion of the vessels to an intestinal loop [Bean (13)]. A reflex vasoconstriction elicited by distension of the gall bladder and mediated chiefly by the right splanchnic nerve has been described by Newman (156). The vagus nerves were not involved in this response.

#### PERIPHERAL VISCERAL EFFERENT SYSTEM, CRANIOSACRAL OUTFLOW

Burstall *et al.* (29) have attempted to produce continuous stimulation of the vagal innervation of the stomach by phrenic-vagus anastomosis in the dog.

The old problem of the nervous control of intestinal movements has been the subject of the presidential address to the physiology section at the meeting of the British Association in Belfast, 1952 by Garry (81). He quotes Bayliss & Starling from 1899: "On no subject in physiology do we meet with so many discrepancies of fact and opinion as in that of the physiology of the intestinal movements," and his survey of the problems certainly indicates that we are in nearly the same position to-day.

The effect of vagotomy and splanchnotomy on gastric motility in the sheep was studied by Duncan (52). Following total vagotomy he observed that the rhythmic activity of the rumen and reticulum and the propulsion of digesta from these organs into the omasum and abomasum were lost. Rumination was also abolished by vagotomy. Splanchnotomy on the other hand did not seem to affect the motility. It was also observed that some activity returned after several weeks, but this was of a different type. TEA<sup>2</sup> was found to depress propulsive motility (157), which was taken to show that the parasympathetic stimuli to the intestine are normally dominant over sympathetic stimuli.

In Hirschsprung's disease, where the distal segment is aperistaltic and aganglionic, Ehrenpreis & Pernow (56) found the amounts of substance P significantly lower than in the controls. In the hyperactive proximal segment more substance P was found than in corresponding segments of the control series.

Many points appear still to be problematic in the mechanisms of gastric secretion. Dragstedt *et al.* (49) reported that in dogs provided with a vagus-innervated total stomach pouch removal of the antrum only reduced HCl-output with 23 per cent, while subsequent crushing of the vagi reduced it by a further 70 per cent. Antrum function and the release of gastrin therefore do not seem essential to vagus HCl secretory function. In other experiments it was found that the low gastric secretion in the dog after antrum excision could be restored if the antrum was transplanted into the colon (50).

Further evidence has been obtained for the postulated preganglionic fibres running in the vagus, controlling intracardiac adrenergic ganglia (110, 128). The role of vagus inhibition in the increase in pulse rate during work and heat has been studied by Craig (37), who concludes that vagal inhibition is less important in man than in the dog in exercise. Bilateral vagotomy inhibited the anaphylactic reactions in the rabbit (147).

Evidence for cholinergic vasodilator nerves to the liver of rabbits was obtained by Ginsburgh, Grayson & Johnson (83). When the arterial pressure was stabilized with the aid of a compensator, depressor nerve stimulation caused an increase in liver blood flow which was blocked by atropine. Schofield (177) showed that the pupillary dilatation obtained after nicotine on the ciliary ganglion was abolished after atropine but uninfluenced by ergotoxine. After section of the third nerve nicotine and acetylcholine had no effect when painted on the ganglion.

#### PERIPHERAL VISCERAL EFFERENT SYSTEM, THORACOLUMBAR OUTFLOW

*Sympathetic ganglia.*—Jabonero (117, 118) describes two different types of synapses in the peripheral autonomous nervous system which are either neuronal or syncytial and postulates different transmission processes in them. In the rabbit, Samuel (173) found that postganglionic sympathectomy diminished or altered the chromidial bodies in 98 per cent of the neurons within the ganglion. Lundberg (140) compared the inhibitory action of epinephrine and norepinephrine on a sympathetic ganglion of the cat and found that norepinephrine was about four times less effective than epinephrine in this respect. This finding is interesting in view of a similar quantitative difference between the two substances on metabolic functions in general (cf. 89). In no instance was he able to demonstrate the facilitation described by other authors. Nor was there any indication of any long-lasting excitatory action from either the presynaptic terminals, or inhibitory preganglionic fibres (120). The inhibitory effect of epinephrine has also been demonstrated on the suprarenal (124). The effect of botulinus toxin on the superior cervical ganglion was studied by Ambache (5) who found a relatively insignificant reduction even with high doses on the response of the nictitating membrane to preganglionic stimulation. A facilitatory action of cardioactive glucosides, especially scillaren A, on the superior cervical ganglion of the cat was observed by Konzett & Rothlin (127). This effect could be demonstrated for acetylcholine, choline, KCl and also to some degree for preganglionic stimulation. The potentiation also occurs after degeneration of the preganglionic fibres and can not be ascribed to inhibition of cholinesterase.

*Sympathetic stimulation and sympathomimetic substances.*—Winbury & Green (203) found that sympathetic stimulation as well as injection of epinephrine, norepinephrine, and ACh<sup>2</sup> lowered the coronary resistance and caused an increased flow in the open-chest dog. The authors found no evidence for active coronary vasoconstriction either by autonomic stimulation or by its chemical transmitters. The sympathetic control of human blood vessels has been the subject of an excellent monograph by Barcroft & Swan (12), largely based on the extensive work of their own and associated groups. The important concept of a critical closing pressure for vessels elaborated by Burton (30a) has proved a useful lead for the study of a variety of vascular reactions. Girling (84) thus demonstrated that electric stimulation of vasomotor nerves raises the critical closing pressure with the degree of constriction within a stimulation frequency range of 0.5 to 25 stimuli per sec.

At a stimulation of 60 per sec. there was only a small difference from no stimulation at all. As a consequence small changes in either the stimulation frequency or the arterial pressure can produce marked changes in the vascular resistance to blood flow. The relation of humoral and vasomotor controls of blood vessels is reviewed by Page (162) who also stresses the importance of reactivity of the vessels especially with regard to the mechanisms of arterial hypertension. Yoshimura & Iida (208) state that low reactivity was often associated with high sympathetic tone. Randall and co-workers (167) analyzed the vasomotor innervation of the dog's hind footpad and correlated vasoconstrictor response to sympathetic trunk stimulation with the inflow of myelinated fibres into it. They arrived at the conclusion that in order to ensure complete preganglionic denervation of the distal portion of the lower extremity of the dog it is necessary to extirpate the entire lumbar trunk as far caudad as L 6 in addition to those fibres which do not pass through the sympathetic trunk.

A number of papers have dealt with the secretory response of the suprarrenal medulla to splanchnic nerve stimulation. Rapéla & Houssay (168) observed that stimulation increased the relative epinephrine release in the dog (cf. 145), and Holtz *et al.* (113) found a release of almost pure epinephrine after splanchnic stimulation in the cat, a result which is at variance with those of others (65, 160). It cannot be excluded, however, that epinephrine-secreting cells may have been activated more or less selectively by splanchnic stimulation.

Daly *et al.* (38) find anew that sympathetic stimulation of pulmonary vasomotors may reduce lung blood flow to a considerable extent; Condorelli (33) maintains that the physiological sympathetic tone in the pulmonary artery is of hardly any significance.

Electrical stimulation of the periarterial nerves to the terminal part of the guinea-pig ileum produced as a rule relaxation of the proximal part and contraction of the distal part (155). Direct stimulation caused a motor response which was first abolished by atropine but later became atropine resistant and of a more sluggish character. The relation of this latter type of contraction might be associated with bradykinin or substance P. Motor effects of norepinephrine are often observed in experiments on isolated intestines.

In her study on the complicated question of uterus muscle response to stimulation, Schofield (178) found that stimulation of hypogastric fibres produced excitation followed by inhibition of the cervix and cornu in the rabbit. This effect could be mimicked by norepinephrine and the author is very likely correct in assuming that it is not a specific effect of epinephrine which would be released in insignificant amounts. Excitatory cholinergic fibres to the uterus were found in about a quarter of the rabbits. Electrical stimulation of the cervix uteri caused pseudopregnancy in over 90 per cent of rats but in less than 26 per cent of mice (183). Muscular reactions of the bladder to electric shock were diminished after section of the hypogastric nerves (136).

Loewe & Puttuck (138) obtained evidence that the major efferent path-

ways of the ejaculatory reflex are sympathetic and the effector organs are adrenergic in the mouse.

An interesting observation showing how an analgesic intraspinally may break the vicious cycle of pathological events associated with vasospastic disease of the leg or diabetic neuropathy has been reported by Galley (77). Norepinephrine was found by Liljedahl (137) to prolong greatly the effect of spinal anaesthesia.

The peculiar disturbance of the reactivity of the skin vessels of the toes in diabetics, showing itself in an inability to dilate maximally after 2-benzyl-2-imidazoline hydrochloride (Priscoline), is not associated with general dysfunction of "peripheral circulation" (99).

A large number of papers have been published concerning the effect of sympathomimetic substances on various visceral functions. There is still some reason to emphasize that the effects of adrenergic nerve stimulation are traceable to norepinephrine. The older concept of epinephrine as the adrenergic mediator is apt to lead to confusion, inadequately planned experiments, and erroneous conclusions.

Infusion of epinephrine either intravenously or intraarterially produces in man a transient vasodilatation of the muscular vessels. This effect is not seen in chronically sympathectomized or denervated forearms as demonstrated by Whelan (200). The sustained vasodilator effect of epinephrine on intravenous infusion is not a direct action on the muscle vessels or a nervous reflex but may be due to metabolites set free by the action of epinephrine.

Norepinephrine, on the other hand, produces neither the initial, nor the sustained vasodilator effect obtained with epinephrine (32) but contracts both skin and muscle vessels. The fundamental difference in the reactivity of the blood vessels in skin compared with those in muscle has also been emphasized by Lanier *et al.* (132). It has been repeatedly claimed that lack of adrenocortical hormones diminishes the response to sympathomimetics. In Addisonian patients Zumoff & Gold (209) were not able to detect any difference in the pattern of response to norepinephrine, however, from the reaction in normals. The actions of intravenous infusion of large amounts of epinephrine and norepinephrine (2  $\mu$ g. base per kg. per min.) seemed to indicate quantitative rather than qualitative differences between the two hormones (90).

The foetal circulation is relatively insensitive to both epinephrine and norepinephrine as demonstrated by Dornhorst & Young (45). A coronary constrictor action of epinephrine, norepinephrine and acetylcholine was observed by Baker (10) on the human foetal heart. Norepinephrine appeared to be 3 to 16 times less active than epinephrine on the amplitude of the beat. On isolated hearts of rabbits, guinea-pigs, and dogs epinephrine and norepinephrine caused identical effects on the same hearts. Both increases and decreases of coronary flow were observed after either drug on rabbits' hearts (134). Similarly Serin (182) did not observe any appreciable differences between the two drugs on the isolated perfused rats' heart. On the isolated papillary muscles of the cat both epinephrine and norepinephrine caused

increased contractile force and automaticity and certain ECG<sup>3</sup> changes (80). A positive chronotropic action of norepinephrine on the denervated heart-lung preparation of the dog was also observed by Gollwitzer-Meier & Witzleb (87). Norepinephrine had a somewhat smaller enhancing effect on the oxidative metabolism of the heart compared with epinephrine. The effect of norepinephrine on the heart *in situ* is largely influenced by reflex vagal tone.

According to Ahlquist & Taylor (1) epinephrine is 2 to 5 times more active than norepinephrine as a renal vasoconstrictor in the anaesthetized dog. On the liver vessels norepinephrine seemed to have a stronger constrictive action than epinephrine (91). The meaning of the shifts observed in threshold to epinephrine on the vessels of the cecal mesentery of the rat are critically discussed by Wiedeman & Nicoll (202).

The volume waves of the spleen after epinephrine administration are interpreted as rhythmically occurring loading and unloading of the organ (112). Gross & Schneider (95) reported that epinephrine and norepinephrine cause a larger rise in arterial pressure when injected into the splenic artery than into the splenic vein. It is suggested that epinephrine releases a substance in the spleen with norepinephrine-like actions. In saline-loaded rats norepinephrine increased the urine flow while epinephrine reduced it (69). Water diuresis in rats was increased by both epinephrine and norepinephrine in the experiments of Dexter & Stoner (43).

In the foetal guinea-pig Munro (154) found that epinephrine as well as norepinephrine caused contraction of isolated segments taken from the two ends of the small intestine. The intervening region was either relaxed or not affected. Epinephrine was found to reduce or abolish the effects of norepinephrine on the foetal ileum.

Certain organs of *Aplysia* and *Holothuria* showed a higher sensitivity to norepinephrine than to epinephrine (64). Whether sympathomimetic amines occur in these animals is so far unknown.

*Denervation and sympatholytics.*—Folkow (73) discusses the factors which determine the value of the constant  $n$  in the flow expression  $F = c \cdot P^n$ , on the basis of experiments on denervated vessels. He concludes that the vascular tone is basically myogenic though strongly influenced by external factors.

Barcroft *et al.* (11) studied the blood flow through rhythmically contracting muscle before and during release of sympathetic vasoconstrictor tone. The effect which could be achieved by slightly raising the body temperature did not alter the blood debt following standard exercises. The conclusion was drawn that the local circulation response to rhythmic contraction is not dependent on an inhibition of nervous vasoconstrictor tone.

After lumbar sympathectomy radiant heat applied to the legs did not elicit reflex vasodilatation in the hands of the patients as reported by Cooper & Kerslake (34). Duff (51) found that the mean vasoconstriction in the hand in response to epinephrine increased fourfold after sympathectomy, the threshold being lowered in 6 of 10 hands. Supersensitivity was observed as early as the sixth day and as late as 12 months after sympathectomy.



In a study of the vasomotor reflexes in the feet Kessel & McPherson (123) found in six of those seven patients with anterior poliomyelitis which showed larger differences in flow between the feet that the lower figure was obtained in the more paralyzed limb. Paus (163) observed that sympathectomy often relieved the vascular disturbances in the feet of such patients.

Berne (16) found no evidence that chronic denervation affects tubular reabsorption of sodium in the dog. The vascular sensitivity is increased (190). It has been concluded that the primary site of hypersensitivity in the denervated kidney is the afferent arteriole. Reabsorption of sodium was not dependent on intact renal nerves (17). No mutual influence between the antidiuresis of epinephrine and of sympatholytic agents was observed by Eränkö & Karvonen (59).

After section of the cervical sympathetic in the rabbit the ascorbic acid concentration ratio in the aqueous humor on the cut side and in the normal side was  $1.11 \pm 0.01$  (14). No difference in milk-secretion was observed in the affected udder half after right lumbar sympathectomy in seven lactating ewes (164).

The possibility of a neurogenic, presumably adrenergic, factor in essential hypertension has led to the testing of the effect of various antisympathomimetics. Corcoran, Taylor & Harrison (35) in a study of this kind found no amelioration of the condition in eight hypertensives after 2 to 26 weeks treatment with dibenzylamine (688-A).

In an interesting study Ohler & Wakerlin (158) found *p*-(2-aminopropyl)-phenol (Paredrine) specifically active in lowering arterial pressure in renal and neurogenic hypertensive dogs, without having effects on the normal pressure.

*Adrenergic mediator inactivating systems.*—The possibility of amine oxidase exerting an inactivating action on sympathomimetics analogous to the action of cholinesterase on acetylcholine has been emphasized by Burn and his associates. Somewhat disconcerting at first sight is the strong increase in action of norepinephrine and corbasil (cobefrin) after denervation of the nictitating membrane, since the weak effect on the normal membrane cannot be due to the action of amine oxidase which does not attack corbasil (71). Burn & Robinson (28) found the amine oxidase content of the nictitating membrane decrease to a minimum of 65 per cent of normal in 10 days after removal of the superior cervical ganglion in the cat. The degree of hypersensitivity was found to be related to the extent of the fall in amine oxidase in a series of 25 cats.

Amine oxidase is present in the earthworm (21) and in *Octopus vulgaris* (20) which is interesting in view of the occurrence of sympathomimetic substances in these animals (62). No amine oxidase was found in *Mytilus* or *Helix*.

The DOPA-DOPA-oxidase system<sup>2</sup> has been considered in the inactivation of catechol amines in pigmented irides *in vivo* (7).

On isolated swine carotid arteries Smith (186) demonstrated a strong immediate sensitization by thyroxine of the constrictive action of epineph-



rine. The effect may be associated with an influence on the amine oxidase system.

*Sympathetic adrenergic mediators.*—Although small amounts of epinephrine are regularly found in extracts of organs and nerves and sometimes obtained in the venous effluent from organs stimulated by their adrenergic nerves, it has never been proven that these nerves release epinephrine. So far, there is only evidence for one adrenergic mediator, norepinephrine, although small amounts of epinephrine may be released concomitantly from chromaffine cells or from other stores.

Cicardo (31) found that the arterial hypertension caused by electrical stimulation of the sympathetic nerves to various organs, by intracisternal administration of potassium, and by central vagus stimulation was antagonized by antisympathomimetics in the same way as norepinephrine. He supposes that in adrenalectomized animals only norepinephrine is released. This assumption is supported by results obtained on adrenalectomized patients (105) where the catechol amine excretion in urine consisted almost exclusively of norepinephrine.

An increased release of norepinephrine from the adrenergic nerves was concluded from the increased output in urine during strong muscular work (66). The increased output of epinephrine was regarded as a sign of adrenal medullary secretion. Outschoorn (161) found larger amounts of norepinephrine than of epinephrine in the effluent from the perfused rabbit's ear whose sympathetic nerves were stimulated.

In human blood (calculated on plasma figures) Weil-Malherbe & Bone (198) found about 0.8  $\mu\text{g.}$  per l. of epinephrine and 3  $\mu\text{g.}$  per l. of norepinephrine while no evidence for "adrenalinogen" or "protein-bound adrenaline" was obtained (197). These figures show very much the same relation between the two catechol amines as in urine. As discovered by Goodall (88) the suprarenal medulla of sheep contains hydroxytyramine (dopamine) in addition to epinephrine and norepinephrine. This finding has been confirmed (184).

The wide variations in different animal species but remarkable constancy of the proportions of epinephrine and norepinephrine in the adrenal medulla of one and the same species is, to the reviewer, a strong indication of specific cells for the production of each of the hormones. Outschoorn (160) reported that general stimulants, such as splanchnic stimulation, acetylcholine or potassium caused an increased release of hormones, but no consistent difference was found in the composition of the hormone mixture after different kinds of stimuli. Insulin, morphine, and tetrahydro- $\beta$ -naphthylamine caused a selective depletion of epinephrine in the rat as previously demonstrated for insulin (115).

Also under other conditions a differentiated secretion of the two hormones can be achieved. Brücke, Kaindl & Mayer (26) showed that hypothalamic stimulation strongly increased the epinephrine release in the cat, while the catechol amine proportion is not changed by carotid occlusion as shown previously. Euler & Folkow (65) compared the effect of various stimuli on the

proportion of epinephrine released in the suprarenal venous plasma in the cat and found that this was about twice as high after sciatic or brachial plexus stimulation as after carotid occlusion, asphyxia or splanchnic stimulation. Stimulation of the suprarenal medulla with 5-hydroxytyramin has been reported by the late Dr. G. Reid (169). The usefulness of the colorimetric method of Euler & Hamberg for the estimation of epinephrine and nor-epinephrine in suprarenal extracts has been established (67). Burn (27) confirms that sustained hypertension in phaeochromocytoma is marked by high urinary excretion of pressor amines and finds that essential hypertension with paroxysms is not, which is in accordance with the reviewer's experience. As to the mechanism of action of sympathomimetic substances it has been claimed (151) that the higher the relaxing effect of a sympathomimetic substance is, the greater is its ability to form lactic acid.

*Axon reflexes and unknown mediators.*—A number of papers have dealt with various types of axon and other reflex phenomena and chemical mediators of antidromic stimulation. The peculiar behaviour of cutaneous vessels has been investigated by Moss (153) and by Dunér & Pernow (54), the sweat glands by Wada and co-workers (195). Girling discusses the venivasomotor reflex (85), and Hilton (107) gives support for the assumption that the post-contraction hyperemia of skeletal muscle is of axon reflex character, mediated by cholinergic fibres in the sympathetic outflow. Job & Lundberg (119) studied the reflex excitation of cells in the inferior mesenteric ganglion on hypogastric stimulation.

Holton (111) found that anticholinesterases reduced antidromic vasodilatation in the rabbit's ear and also the vasodilator response to spinal root extracts. Further contributions to this field have been made by Hellauer (103) and by Umrath (194).

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## HIGHER FUNCTIONS OF THE NERVOUS SYSTEM<sup>1,2,3</sup>

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The inclusion of this chapter is a new departure, beginning with that of Harlow, who last year chose to survey the very important field of cortical localization of intellectual functions (1a). This field was so thoroughly and ably reviewed by Harlow that the present reviewer has decided to omit it and to concentrate on other topics. References to literature on cortical localization of intellectual functions (and to some related papers) which have appeared since Harlow's review are listed (94 to 126).

History of science has shown again and again that development of an important new method is followed by crucial, and often epoch-making discoveries. Development of the microelectrode which can penetrate and record from within a single nerve cell is the most recent example of such methodological advance. Discoveries stemming from the development of this new technique by Eccles and his co-workers are described by Eccles in his excellent book, entitled: *The Neurophysiological Basis of Mind. The Principles of Neurophysiology* (1).

Granit (2) has reviewed this book from the standpoint of a neurophysiologist. He says,

A great step forwards in the analysis of synaptic excitation and inhibition came with the recent work by Brock, Coombs & Eccles (3) in which they inserted an internal microelectrode into the ventral horn cell and found monosynaptic excitation and inhibition to be accompanied by post-synaptic potentials of depolarization and hyperpolarization respectively, which followed the known time course of monosynaptic excitation and inhibition.

Inhibition is a concept of major importance for any behavior theory. Eccles' new findings with respect to inhibitory phenomena at the synapse cannot fail to have strong influence on psychological theory. These findings signify, of course, that synaptic inhibition is a phenomenon in its own right, and not somehow merely a by-product of excitation. At the synapse, inhibi-

<sup>1</sup> This review covers the period approximately from 30 June 1952 to 30 June 1953. The writer wishes to express his gratitude to Miss Daisy Casdim, Miss Elfriede Herfert, and Mrs. David Hubel for their assistance in its preparation.

<sup>2</sup> The following abbreviations have been used in this chapter: CS (conditioned stimulus); USC (unconditioned stimulus); CR (conditioned response); UCR (unconditioned response); CC (convergence center); EEG (electroencephalogram); EMG (electromyogram).

<sup>3</sup> This chapter was prepared with the assistance of the Medical Research and Development Board, Office of the Surgeon General, Department of the Army, under Contract No. DA-49-007-MD-70.

tion is an active hyperpolarization process in the surface membrane of the motoneurone. Moreover, this hyperpolarization may be regularly and predictably produced in the motoneurone by stimulating its inhibitory branch of the nerve in the reflex preparation for study of reciprocal innervation (1, p. 172).

Sometimes behavioral observations suggest (even demand) the presence of certain physiological mechanisms before they are discovered by the physiologist. Something like this seems to have occurred here. Psychological analysis of conditioning showed that inhibitory phenomena could not be accounted for solely in terms of excitatory principles. This analysis was rooted historically in some keen observations of Pavlov which have been many times confirmed in various conditioning experiments of the American school. Pavlov found that the "inhibitory" effects of the procedure of experimental extinction, repeating the conditioned stimulus without paired presentation of the unconditioned stimulus, diminished with time when the animal was kept in its cage without presentation of either CS<sup>2</sup> or UCS<sup>2</sup>. He called this "spontaneous recovery of the conditioned reflex." In analyzing phenomena of experimental extinction, Hilgard & Marquis (4) concluded that at least two principles were required: interference ("a process in which old learning is antagonized by new"), and adaptation, a process of inhibition whose strength is a direct function of frequency and rate of repetition. It was further postulated that adaptation is not permanent. The phenomenon of spontaneous recovery was one thing which made it necessary to posit the process of adaptation, because spontaneous recovery could not be accounted for in terms of the principle of interference (4, p. 118).

There is a second line of evidence against the interpretation of extinction as interference from new learning. Even with continued reinforcement (CS followed by UCS) the conditioned response (CR) will lose strength under certain conditions, the main one being "massing of trials" (many trials with only brief intervals between paired presentations). Such a phenomenon cannot be accounted for other than in terms of an active inhibitory process produced by repeated reaction, the process which Hilgard & Marquis called "adaptation." Hull (5, p. 278) has incorporated this process in his behavioral system, giving it the symbol  $I_R$  (reactive inhibition), and this term rather than "adaptation" has come more into common use.

Just as Sherrington inferred from his observations of the reflex preparation that there must be a central inhibitory state, independent of central excitatory state, so Hilgard & Marquis inferred from observations of conditioning in intact organisms (human as well as animal) that there must be an independent inhibitory process (adaptation). The historical importance of Sherrington's work in relation to this problem in the field of conditioning is shown by the author's references to Sherrington's early work on reflex adaptation (4, p. 105) and to his basic work on reciprocal innervation (4, p. 109).

Before turning from this problem to consider Eccles' model of the conditioned reflex, it is useful to keep in mind Eccles' own work on repetitive stim-

ulation, his work on posttetanic potentiation. Eccles has evidence which strongly suggests that "the presynaptic impulse becomes a more effective synaptic excitator (or inhibitor), because repetitive stimulation temporarily alters the spatial relationship of the synaptic knobs to the post-synaptic membrane" (1, p. 198). Note especially that inhibitory, as well as excitatory reflex effects are strengthened by repetitive stimulation. We must be cautious in applying these findings directly to more complex phenomena (such as "internal inhibition" of Pavlov) because it has not been shown that repetitive stimulation can change the direction of effect from excitation to inhibition in the monosynaptic preparation. But inherent in these findings is a possible mechanism for the phenomenon of reactive inhibition (or adaptation). Repetitive stimulation would have the effect of progressively increasing the inhibitory state (hyperpolarization). If such repetitive (or any repetitive) stimulation had a differential effect, such that it increased inhibitory state (made synaptic inhibition more effective) more than or faster than it increased excitatory state, we would have a simple and accurate mechanism of adaptation (or reactive inhibition) at the neurophysiological (or reflex) level, at least.

Most of the considerations which have thus far engaged our attention will be useful now in the consideration of Eccles' model of the conditioned reflex (his "neurophysiological hypothesis of conditioned reflexes"). Very logically, he proceeds from one of the major findings of his experimental program, the finding that repetitive stimulation produces prolonged plastic changes at synapses (1, p. 219). These findings, he says, make unnecessary the improbable postulate of dynamic patterns of circulating impulses that continue during sleep, deep anaesthesia, concussion, and convulsive seizures. He does, however, bring in prolonged reverberatory activity occurring in the neuronal network, to explain how a single event (CS and UCS combined) may activate each link in a spatiotemporal pattern thousands of times within a few seconds. He notes that Hebb makes a related postulate when he supposes that "a reverberatory trace might co-operate with the structural change, and carry the memory until the growth change is made."

The model is a very ingenious one and, more than any other such model which has been proposed, is undoubtedly sound in every respect from the point of neurophysiological fact. The model involves neural networks rather than the single neurone type of diagram which has often been drawn in the past. Connections are shown by columns or bands rather than by single neurones. The way propagation along each such column, particularly in the neuronal network, would occur is shown in an ingenious diagram: two drawings of the same neuronal network, showing a different response to a changed input (1, pp. 220-22). In addition to the usual CS, UCS, and R (response), there are two centers: there is, firstly, the receiving center (RC) which receives impulses from UCS; this is the center for the unconditioned reflex. The second, or convergence center (CC) receives afferent impulses from both pathways (CS and collaterals from UCS). The discharge of impulses from

CC<sup>2</sup> will develop a special spatiotemporal pattern of impulses in the neuronal network, which he diagrams as a path which is part of the NN (neural network) column. He goes on to show how such a system can account for acquisition of a CR<sup>2</sup> which is, incidentally, not quite the same as UCR<sup>2</sup> (which conforms to behavioral fact).

Eccles' analysis of the acquisition aspect of conditioning seems correct. But his account of experimental extinction does not appear to be in line with the behavioral facts. He says,

Thus with CS alone there will be progressively less activation of synaptic knobs in the neuronal network, which will consequently regress; and so an explanation is provided for the gradual extinction of a conditioned reflex when it is not continuously being reinforced by the unconditioned stimulus (1, pp. 224-25).

This, of course, is the situation where, to use the familiar Pavlovian example, the tone is sounded again and again without introducing meat powder into the dog's mouth, following the tone. It is true, as Eccles says, that in this situation there is progressive weakening of the conditioned reflex, and thus far there is nothing wrong with his analysis. But what happens if, instead of presenting the tone without meat powder, we just leave the animal in its cage and do not present the tone at all for a long period of time? Applying Eccles' principle of disuse (1, p. 224 f.) shouldn't we expect this situation to produce even more rapid weakening of the conditioned reflex than the first situation (tone without food)? But this is exactly opposite to what actually occurs.

In the absence of experimental extinction (CS presented without UCS) CR's persist for very long periods—months, years (4, p. 129). Repetition of CS is necessary to produce a significant weakening of reaction and following extinction, failure to present the CS will actually lead to a strengthening of this reaction (spontaneous recovery). All the phenomena of reactive inhibition (adaptation) which we have discussed are so important in conditioning that it is extremely desirable to have a model which can handle them.

Eccles' own extremely important work on inhibition appears neglected in the construction of this model. Principles derived from this work would appear indispensable to account for elementary behavioral phenomena of conditioning. The observations concerning disuse will undoubtedly be useful [see McGeoch (7, p. 453)] but not in the classical conditioned reflex, primarily, because it is just here that disuse is associated with least change (or change in the direction opposite to that which the model proposes). It is probable that some combination of "usage-disuse" with depolarization-hyperpolarization could handle the two aspects of conditioning quite well. As suggested earlier in this review (with caution) "usage-hyperpolarization" might be suggested to account for the weakening of reaction with repeated stimulation (reactive inhibition). Ordinary experimental extinction would come in this category. "Hyperpolarization-disuse" might be suggested to account for spontaneous recovery (this would seem to require a more rapid rate of regression for the inhibitory than for the excitatory component).

In sum, the model, while accurate and true to neurophysiological fact, and while definitely useful in suggesting how simple learning may take place (a very real positive contribution for which psychology has been waiting many years) is nevertheless defective in accounting for one basic aspect of the conditioning process. But the missing parts (needed to correct the defects on the inhibitory side) appear to be "lying on the table" in the products of the brilliant experimental work of Eccles and his co-workers on the phenomena of inhibition.

#### STRUCTURAL BASIS FOR LEARNING

In the matter of the experimental work bearing on the question of structural basis for learning (see 1, p. 227 for general statement), the data add significant strength to the kind of learning theory which Hebb (8) has developed. Hebb's theory may be designated a "place" theory in contrast to a "dynamic" theory, like Lashley's. The reader is directed to p. 266 of Eccles' book for the incorporation of the "best" features of Lashley's argument in a model of "memory" which represents, basically, a place theory of higher functions. Engrams are spatially represented with a margin of safety factor in multiple representation.

Crucial to such a model is the place of critical synaptic strengthening with use (repetitive stimulation). This is not the simple reflex arc theory which Lashley demolished. This is a much more complex model in which each "place" of critical strengthening is a part of an intricate pattern which is multiply represented. The engram is visualized, not as a circumscribed place, but as an organized extensive neuronal pattern like "lattice work," and with reduplication of its essential features in other lattices.

Eccles' approach to the mind-brain problem is dualistic. The reviewer's is monistic. This difference in postulates is in the realm of philosophy and there is not space to deal with these questions here.

#### REACTIVE INHIBITION

*Animal experiments.*—Teichner (9) and Teichner & Holder (10) have reported rat learning data consistent with Hull's principles of reactive inhibition and stimulus generalization, and opposed to interference-type theories. Need for some reformulation of Hull's theory of extinction has been claimed by Kimble & Kendall (11), who found that extinction was more rapid in a group of rats subjected to extinction by a toleration method in which the conditioned stimulus was introduced gradually. In the control group extinction was accomplished by the conventional procedure of presenting the conditioned stimulus at full intensity without the shock.

*Motor learning in human subjects.*—In pursuit rotor learning, time on target has been found to increase markedly with interpolation of a brief rest period. This well established phenomenon is called "reminiscence" and has usually been conceptualized as dissipation of reactive inhibition. Ellis, Montgomery & Underwood (12), in reviewing recent research on reminiscence in motor tasks, state that amount of reminiscence is proportional to length

of interpolated rest, number of prerest responses, and degree of massing of prerest trials.

Grice & Reynolds (13) investigated the motor specificity of the reminiscence effect. Was it confined to the situation in which one arm was used throughout, or would the effect transfer to the nonused arm? In one experiment subjects practiced with the left hand before and after the rest (LL condition), while in the other experiment they employed the right hand before the rest and the left hand afterwards (RL condition). Gain over predicted massed practice scores was an increasing function of amount of rest for both conditions. The LL groups showed larger gains. The authors suggest "that the gains in bilateral transfer indicate the presence of temporary inhibitory factors either associated with generalized postural adjustment or of a perceptual or central character."

Bartoshuk, in our laboratory (14), has data from experiments on mirror-drawing which may have some bearing on the findings of Grice & Reynolds. His electromyographic studies show that muscle tension in both forearms increased progressively and linearly from the beginning to the end of each separate mirror-drawing task. It seems possible that these muscle tension gradients in the passive arm (which would not have been detected in the absence of electromyography) may represent mechanisms involved in the bilateral transfer effects described by Grice & Reynolds.

Ellis, Montgomery & Underwood (12) studied the effect of effort on reminiscence by varying the work-surface height. With regard to this question results were negative, although evidence favoring inhibition theory was found: for both heights, reminiscence increased with increases in amount of prerest practice; for both heights, reminiscence was markedly decreased at the long (24 hr.) rest. Test of the two-factor theory of inhibition, in which reactive inhibition is distinguished from conditioned inhibition, is reported by Kimble & Shatel (15) who infer from their pursuit rotor data that reactive inhibition decreases to zero late in practice and that conditioned inhibition increases with practice in a negatively accelerated fashion. Bilodeau (16, p. 112) reports results which he believes limiting with respect to properties which may be ascribed to conditioned inhibition in motor behavior. The relation of reactive inhibition to "warming-up" phenomena has been studied by Silver (17) and by Adams (18).

*Rote learning.*—The rote learning studies most relevant to the problem of reactive inhibition are those of Underwood (19 to 23), who has undertaken a systematic series of investigations of distributed practice. The papers cited comprise numbers 7 to 11 in his series. According to the Hull-Hovland theory (19, p. 86), recall following massed practice should be better than following distributed practice, provided that the massed and distributed groups were at equal levels at the completion of original learning. This follows from the part of the theory based on reactive inhibition, that with a rest interval inhibition from massed learning will have dissipated, thus leaving it superior (in recall) over material which was learned under the condi-

tion of distributed practice. In three separate experiments, Underwood found superior recall under the condition of learning with massed practice. Hovland himself obtained contrary results, opposed to his own theory (19, p. 85). Underwood's experiments led him to conclude that the difference between Hovland's results and his own could not be accounted for on the basis of length of intertrial interval defining distribution, and believes that the differences between the studies may result from the fact that Hovland's subjects were much more highly practiced. He is presently investigating this possibility.

Among the other papers on rote learning there are three of particular interest. Two deal chiefly with inhibition through interference (as distinguished from reactive inhibition). Intraserial interference was analyzed in some very ingenious experiments by Deese & Kresse (24). They concluded that the classical skewed serial position effect reproduced in their experiments could be accounted for largely by two empirical factors: intralist intrusions that were almost symmetrically bowed, and failures to respond that increased through the first half of the list and reached a plateau during the second half. Postman's (25) comparison of recall and recognition methods in retroactive inhibition suggested that superior retention by the recall method, which has generally been found, may be in part a methodological artifact produced by keeping the opportunities for interlist interference to a minimum. Using a multiple choice recognition test, in which each correct recognition required discrimination between an original and interpolated syllable, he found significantly more retroactive inhibition than with the kind of recognition test ordinarily used, although not as much as with the recall method of testing retention. In Hovland's paper (26) on prelearning syllable familiarization the introduction of concepts from "communication theory" is of particular interest.

#### DRIVE AND REINFORCEMENT

The theory that drive reduction is essential for learning is presently under attack from several quarters, and this attack is being countered by proponents of the theory. As evidence against the theory Bitterman, Reed & Krauskopf cite their finding that galvanic skin response (GSR) conditioning and extinction are unrelated to the duration of the unconditioned stimulus (27). Data from discrimination-learning experiments in the monkey led Butler (28) to hypothesize a visual-exploration motive which "is strong, persistent, and not derived from, or conditioned upon, other motivational or drive states." This is not opposed to the drive reduction position, but it does represent evidence against the view held by some that secondary drives are invariably derived from basic tissue needs such as hunger, thirst, and avoidance of pain. Carper (29) reasoned that if primary need is a basic factor in learning, glucose should have a higher reinforcing value than saccharin. He states that this assumption was not borne out by the data on resistance to extinction in his experiment.



Miller and his co-workers are engaged in a series of experiments to analyze the mechanism of satiation and its relationship to the rewarding effects of food. They present data which support the drive-reduction hypothesis. Using a consummatory response (amount of milk drunk) to measure hunger, Berkun, Kessen & Miller (30) obtained results confirming previous work. They found that milk injected directly into the stomach produced a prompt reduction in hunger, but that milk taken normally by mouth produced an even greater reduction. In a second experiment, Miller & Kessen (31) found that milk injected directly into the stomach can serve as a reward to produce learning, and that milk taken normally by mouth serves as a stronger reward to produce faster learning.

The phenomenon of "latent" learning (a sudden drop in errors on the day following a single rewarded run in rats which had been running a maze without food) has been used as an argument against drive reduction theory. Two experiments by drive reduction theorists have yielded further data on this problem of latent learning, and in both instances it was claimed that the effect could be at least partly explained in terms of drive reduction [Muenzinger & Conrad (32); and Meehl & MacCorquodale (33)]. The fact that rats will learn a response that turns off a light but not one that turns on a light is offered by Zeaman & Radner (34) as evidence in favor of Hull's reinforcement theory, as opposed to Guthrie's, but it is stated that the crucialness of the data depends upon the outcome of further research on the nature of the rat's unlearned response to light.

#### ANXIETY CONSIDERED AS A DRIVE

The topic of anxiety in all its experimental and clinical aspects is enormous, and badly in need of comprehensive review, which is not possible in a summary such as this. Investigations concerned with the drive-properties of "anxiety" are prominent in current literature on learning [Rosenbaum (35)]. "Anxiety" in animals is generally inferred from fear reactions to stimuli which have been associated with shock. However, intercorrelations among commonly used measures of fearfulness appear very low [Bindra & Thompson (36)]. Further evidence for a two-factor theory of the role of shock in reinforcement has been obtained by Gibson (37). The experimental program of Brady, Hunt, and their co-workers (38 to 41) investigating the effect of electroconvulsive shock on a conditioned emotional response (CER) has led to a number of important findings of theoretical interest and of great value also in clinical aspects of the problem. Their admirable practice of using an operational designation (CER) instead of "anxiety" should be noted.

With human subjects in rote learning experiments the measure of "anxiety" has generally been derived from questionnaire data [Mandler, Sarason and their co-workers (42, 43, 44); Lucas (45); Montague (46); Taylor & Spence (47)]. Bitterman & Holtzman (48) in their conditioning study, employed other clinical procedures in addition to questionnaire. In the conditioning study by Spence & Taylor (49), where psychiatric patients were em-

ployed, there was the implication that "psychotics" were higher in level of anxiety than controls. But this is questionable on clinical grounds. In any case, there was need for a more detailed description of the clinical material.

While investigators have usually been careful in describing their measures of anxiety, there is a danger, nevertheless, that constant use of the term will convey false impressions concerning unitariness of the anxiety variable. Correlation studies of measures of anxiety are sorely needed.<sup>4</sup> At the present time it would appear much safer to use less pretentious designations, denoting actual scaling or rating procedures. In the matter of using the term "anxiety" in his experimental reports, the present reviewer may also be criticized because even in a psychiatric setting where the range of personality deviations is far wider than in the general population, and where detailed case histories are available, the term should be used with extreme caution.

Theorists of the Hull-Spence school hypothesize that the Taylor Anxiety Scale measures drive, and it is important to review the experimental evidence bearing on this question. Neither rapid eyelid conditioning nor poor performance in complex learning tasks is particularly crucial for the drive theory. Poor performance on learning tasks can easily be accounted for in terms of interfering (disorganizing) effects of psychoneurosis [Montague (46)]; and superiority in conditioning with nociceptive stimuli as UCS [Spence & Farber (50)] can be handled by postulating a higher intensity value of the UCS [see Spence (51)] for psychoneurotics. Experiments in our laboratory strongly suggest that patients who complain of persistent feelings of tension and strain, irritability, unremitting worry, restlessness, and inability to concentrate may also be particularly sensitive to pain.

What is much more crucial for the theory is the question whether subjects scoring high on the Taylor Anxiety Scale are superior to low scorers on the Scale in simple learning tasks. There is indeed some positive evidence on this point [Montague (46); Farber & Spence (52)], but it seems to this reviewer that stronger evidence is both expected by the Hull-Spence theorists themselves and really required for convincing demonstration of this very important point.

There is a group of psychiatric patients who manifest a tensional state of such severity that work efficiency is interfered with to the point that medical advice is sought, and which is characterized by one or more of the following complaints: persistent feelings of tension or strain, irritability, unremitting worry, restlessness, inability to concentrate, feelings of panic in everyday life situations. One may adopt the pathologist's approach in the study of patients in which such a picture predominates. Objective descriptive studies along this line are of great value at the present time, and one may speak of such a group as being very high in "tension." Quantifying degree of

<sup>4</sup> A recent unpublished dissertation by Thomas Howard at Tulane University has shown absence of significant correlation among three commonly used measures of anxiety: psychiatric diagnosis, Rorschach indices, and palmar sweating.

"tension" within the group is exceedingly difficult. There have been some recent attempts to achieve this kind of quantification within the dimension of "tension." Ulett *et al.* (53) report a correlation of 0.51 between EEG<sup>2</sup> indicators and clinical criteria of what they have called "anxiety-proneness." EEG response to intravenous sodium amytal as a quantitative indicator of "tension" in psychiatric patients has also been investigated [Shagass & Malmo (54); Shagass (55)]. High correlations were found between clinical ratings of tension and an inflection point in the rising curve for fast frequency components of the EEG during sodium amytal administration. The inflection point was defined as that point which followed an abrupt rise and preceded a clear plateau in the curve. The amount of sodium amytal required to produce this inflection in the curve provided an objective threshold value. It was found that this EEG threshold point usually coincided with onset of slurred speech. Persky, Gamm & Grinker (56) report significant correlation between fluctuation of "free anxiety" and quantity of hippuric acid excretion.

#### ANXIETY IN RELATION TO THE SLEEP-WAKING CONTINUUM AND THE GENERAL PROBLEM OF LEVELS OF CONSCIOUSNESS

Electrophysiologists and allied workers are concerned with objective correlates of different stages in the continuum of "consciousness," from deep sleep, or coma, to alert attentiveness (or strong excited emotion). Lindsley's activation theory of emotion (57) is based on correlations of EEG data and psychological states (58). In his schema "anxiety" is at one end of the behavioral continuum. This kind of approach to psychological problems is particularly important just now because it may increase our understanding of relationships between activities in the newly discovered reticular mechanisms of brain stem and thalamus, and behavior. In his theory of emotion, Lindsley emphasizes the activation aspect of reticular functioning. Jasper (59) has taken pains to elucidate mechanisms of reciprocal action in the reticular system and their possible role in integrating (or regulating) functions [Jasper & Ajmone-Marsan (60)].

From the historical point of view it is important to note that Penfield, in his Harvey Lecture (61), predicted on the basis of his clinical observations that such subcortical mechanisms must exist; and although the importance of his theories extends far beyond the topic which we are considering (and the same thing is true of Jasper's work) it is useful to refer to them here. With regard to the reticular system, Penfield (62, p. 513) has recently stated:

It is seen now that the intralaminar system of the thalamus and the reticular system of the brain stem are parts of a neurone complex with widespread connections to both hemispheres, connections that would make possible the central organization of function in the cerebral cortices.

Penfield then goes on to define his centrencephalic system

as that central system within the brain stem which has been, or may be in the future, demonstrated as responsible for integration of the function of the two cerebral

hemispheres. The centrencephalic system would not, thus, include the cranial nerve nuclei nor other subcortical structures the function of which is related solely to one cerebral hemisphere (62, p. 514).

It should be noted that Penfield accepts Herrick's definition of brain stem, which includes the thalamus. On the basis of evidence found in study of epileptic automatism, Penfield tentatively subdivides the centrencephalic system into two mechanisms, the "A-Mechanism: used to record a man's current perceptions"; and the "B-Mechanism: used in the integration of the sensory and motor systems, the acquired skills of speech and manual dexterity, and in recollection of past experience" (62, p. 526).

Other experimental investigations of phenomena related to the behavioral and conscious continuum are further studies of arousal mechanisms [Li, Jasper & Henderson (63); see also Jasper (64) for a comprehensive summary of this whole topic and for a discussion of the significance of alpha rhythm conditioning; Bernhaut, Gellhorn & Rasmussen (65)]. On the other end of the continuum, experimental work on sleep was reported [Monnier (66); Hess, Koella & Akert (67); Wyke (68)].

Kety has summarized his very important data on metabolism of the brain in relation to the problem of consciousness (69, 70). He found no change in oxygen consumption of the brain with mental work nor during natural sleep. He believes that a state of apprehensiveness may be associated with increased oxygen consumption of the brain (though he feels the evidence incomplete). Photoelectric oximetry has been used by Doust & Schneider (71) in the study of sleeping habits of seven normal healthy subjects. Seven planes of sleep were suggested, and the various physiological concomitants of sleep closely resembled those accompanying states of anoxemia.

#### PHYSIOLOGICAL RECORDING IN CONDITIONING, LEARNING, AND ATTENTIVE STATES

Notterman, Schoenfeld & Bersh (72) have described a technique for establishing a conditioned heart rate response in human subjects. CS (tone) when paired with UCS (shock) elicited a conditioned response (fall in heart rate), although response to shock alone produced a rise. Data on respiration were not given, and one wonders whether the paradoxical reversal in direction of change of reaction for conditioned and unconditioned response might be somehow related to factors of respiratory phase. Even if this were so it would not alter the importance of the finding, but only add to our information about the total process involved. Freedman (73) has recently reviewed respiratory conditioning, and reported his own findings in dogs. In a second study (74), Notterman and his co-workers have demonstrated for the first time that an autonomic conditioned response is more resistant to experimental extinction with the method of partial than regular reinforcement. In a third study (75) these workers compared three extinction procedures following heart rate conditioning: (a) ordinary extinction without instructions concerning absence of shock, (b) with instructions, and (c) instructions plus the stipulation that shock would be omitted only if they made a specific

motor response (tapping a telegraph key) whenever the conditioned stimulus was presented. Extinction was more rapid under both instructed conditions than when no instructions were given prior to extinction, but the most rapid extinction was obtained in the instructed-avoidance group.

Henderson (76) tested Dunlap's hypothesis that practice in a simple reaction-time (RT) situation will result in progressive decrease of muscular contractions in nonparticipating body parts at the moment of each reaction. The right arm was active in performance, and electromyographic recordings were made from muscles of the "inactive" left arm. No recordings were taken from the right arm. Although electromyographic activity was found to decline during the first four days of practice, absence of data for the right arm makes this part of the study inconclusive, as decline of tension in nonparticipating body parts relative to tension in the active arm would appear to be the crucial point.

Meyer, Bahrick & Fitts (77) found that offering incentives to subjects in a pursuit task increased their blink rate, and it was proposed that blink rate might be used as an index of generalized muscular tension. Using the method of electrical skin changes, Taylor (78) obtained evidence for differential reaction to subliminal visual stimuli, as a function of prior reinforcement. Ellis & Brighthouse (79) in studying the effects of music on respiration and heart rate published some interesting curves, showing rising gradients in respiratory rate during listening to music. These resemble some similar gradients from physiological recordings which we have seen in our laboratory, in subjects listening to recorded talking. Mowrer and his co-workers are studying palmar perspiration in patient-psychotherapist relationships. They employ a colorimetric method [Mowrer (80), p. 618].

#### EFFECT OF EARLY EXPERIENCES ON ADULT LEARNING

According to Hebb (8) early learning is much slower, and in some respects almost irreversible in its effects. Hymovitch (81) studied in the rat the effect of varied infant environments upon adult problem-solving ability. Superiority of the rats reared in free environmental situations over those reared under restricted circumstances was clearly shown. Two further experiments confirming and extending these observations have since been published [Bingham & Griffiths (82); Forgays & Forgays (83)]. Additional support for the theory has been obtained by Forgays (84) in a study of differential word recognition with children. Tachistoscopic recognition of words exposed to the right was found to be significantly greater than for words presented to the left of fixation, and the superiority of recognition of words presented to the right of fixation over the left was significantly related to educational grade level. The results were felt to be confirmatory of a selective retinal training and in conflict with the theory of a general equipotentiality in vision. A related problem of fear as reaction to the unfamiliar or strange (as distinguished from conditioned fear reaction) was studied in the dog by Melzack (85). Negative results were reported by Griffiths & Stringer (86)

who failed to find any significant effects of intense stimulation of rats during infancy (intense auditory stimulation, rapid rotation, extremes of environmental temperature, and shock on an electric grid) on adult behavior as measured by learning tests, measures of emotionality, and susceptibility to sound-induced convulsions.

DELGADO'S EXPERIMENTS ON RESPONSES EVOKED IN THE  
WAKING CAT BY ELECTRICAL STIMULATION OF THE  
MOTOR CORTEX

It is perhaps presumptuous on the part of the reviewer to designate one set of experiments as the single most important experimental contribution of the year to the subject of "Higher Functions of the Nervous System." But the temptation is very strong to make this statement about Delgado's experiments (87). As far as this reviewer is aware, these experiments have demonstrated, for the first time, the fact that actions having the essential mark of voluntary, purposeful behavior (8, p. 145) may be elicited by electrical stimulation of the motor cortex. Delgado says:

... movements were in general dextrous, and the whole body participated to facilitate the response. In several experiments the evoked activity was not only dextrous but also purposeful. Directed licking, avoidance of obstacles, or drinking of milk under the influence of electrical stimulation are some examples.

In these cases, the theories of localization in the motor cortex (muscle representation—mosaic or focal—or movement representation—punctate or focal) do not completely explain the observed phenomena. Stimulation of the same cortical point always produced the same *action*, for example licking; but the movements of the head and body were different. Sometimes the cat turned to one side to lick himself, or tried to lick our hands. *Movements varied, the action remained constant*. Our stimulation evoked something more elaborate and better co-ordinated than simple tongue movements (87, p. 444).

Other conclusions were:

The intensity of motor responses evoked by stimulation of a cortical point increased in relation to the state of the animal, from sleep to moderate activity. Strong spontaneous activity, as jumping, either decreased the cortical excitability or blocked pathways. Thus, the motor effects of electrical stimulation were abolished. This mechanism may play a role in avoiding disturbing influences upon important and energetic activities. . . . Activation of the motor cortex by spontaneous activity or by electrical stimulation seems to have a similar functional value. Natural and artificial stimuli may interact by summation or inhibition according to their respective intensities and locations. . . . Stimulation of the motor cortex did not appear to cause pain, disagreeable sensations or emotional disturbance of the animals. Motor response of the face did not alter walking of the cats. This is in striking contrast with emotional changes associated with stimulation of some areas of the temporal lobe (87, pp. 445-46).

In this reviewer's opinion, Delgado, in this brilliant experimental work, has produced facts which will spare no theorist of brain function the work of revising, or, at the very least, expanding his theory.

Space does not permit an account of further important current work by Delgado and his co-workers [Delgado & Rosvold (88); MacLean and Delgado (89); see also Kubie (90) who attempts to integrate Penfield's work on the temporal lobes (91) with this and with psychoanalytic concepts; Delgado & Anand (92)]. Some of these papers have been reviewed by Fulton (92a) in the 1953 *Annual Review of Physiology* [see also MacLean (93)].

#### BEHAVIOR DEVIATIONS

*Stress.*—Lazarus, Deese & Osler (127) in their review speak of "psychological stress" and in a footnote refer to Brown & Farber's (128) concept of frustration, indicating essential agreement with the views expressed in Brown & Farber's paper which had not been available to them at the time of writing. It would appear desirable to use a term such as frustration instead of psychological stress for the phenomena dealt with, and to reserve the term "stress" for the kind of phenomena with which Selye (129) deals.

*Conflict.*—In our laboratory we have applied the electromyographic method to the study of conflict in hysteria (6), in tensional headache (130) and in psychotherapeutic interview (131). Our EMG<sup>2</sup> data have led us to believe that mechanisms of central conflict may, under certain circumstances, reveal themselves in muscle potentials.

Bailey & Miller (132) report data on approach-avoidance conflict in cats, in which sodium amytal appears to produce a greater reduction in the fear motivating avoidance than in the hunger motivating approach. They cite Masserman's work and suggest that conflict data of this sort may be accounted for without introducing the concept of psychoneurosis.

*Bodily physiology in "emotional" disorders.*—Altschule's book (133) should be a valuable source of references for workers in this field. His approach is empirical, in the main, although he does present his views regarding problems of etiology.

He states, "Although there is ample evidence that emotion aggravates most diseases, there is no proof that it *causes* any; such conditions as peptic ulcer, ulcerative colitis, hypertension, bronchial asthma, and rheumatoid arthritis must be considered disorders of unknown etiology" (133, p. 210). With regard to bodily function in manic-depressive, involutional, and schizophrenic psychoses, he classifies the material, in summary, under four main headings, one of which is: "Manifestations of adrenocortical hyperactivity, probably both cause and effect of the psychotic state, and found only early—the late disappearance of which suggests that adrenocortical hyperactivity has only a precipitating role in psychosis and is not central to the etiology of these diseases" (133, p. 216). With regard to data on bodily function in neurosis, he states, "These facts surely do not warrant a sweeping conclusion, but they do raise the possibility that both the psychologic and the visceral instabilities are consequent to a defect in the regulation of neuronal function in the brain" (133, p. 211). Altschule did not attempt any systematic consideration of the function of the brain.



Beach has argued along somewhat similar lines:

There is no necessity for postulating a "psyche" which acts upon the animal's "soma." If the gastric acidity is increased under certain experimental conditions, the investigator seeks the causes for this change in other aspects of his subject's physiology, perhaps in the brain stem, the hypothalamus or the cerebral cortex . . . . The "psychic" element in actuality consists of activities within the nervous system (134, p. 273).

Current research in this field has also been summarized by Wolff (135) and Wolf & Wolff (136). Mahl has reported two more investigations on chronic fear and gastric changes (137, 138); Holmes & Wolff (139) have carried out an electromyographic study of patients with backache; and Malmo & Shagass (140) have described their work on arterial pressure in psychiatric patients. Grace & Graham (141) have dealt with the matter of the patient's attitude in relation to particular symptoms or diseases.

Lacey and his co-workers (142 to 145) have been carrying forward a program of study, dealing with what they call "response specificity," which they relate to the concept of "symptom specificity." This work has been of considerable value in showing that normal individuals (like patients) differ from one to the other, significantly, in peak reaction to various stimulating conditions: "for a given set of autonomic functions individuals tend to respond with a pattern of autonomic activation in which maximal activation occurs in the same physiological function, whatever the stress" (145, p. 21).

On the basis of recent work, they have revised their hypothesis somewhat from its earlier form:

The revised hypothesis is: For a given set of autonomic functions, there exists quantitative variation among individuals in the degree to which a pattern of response is stereotyped. Some individuals are so constituted that they will respond with a given hierarchy of autonomic activation whatever the stress; others will show greater fluctuation from stress to stress, although they will exhibit one pattern more frequently than others; still other individuals randomly exhibit now one pattern, now another (145, p. 21).

*Adrenocortical physiology and behavior.*—This has been an active field of research of late. During the past year a number of interesting reports have appeared [Cleghorn (146); Browne (147)—see also usefulness of personality tests, p. 199; Lidz *et al.* (148); Berkeley (149); Hoagland (150)]. In addition, Altschule's critical review should be seen (133, pp. 178–85). The Malamud-Hoaglund Rating Scale (for behavior) has been found very useful in this area of work (151, p. 225).

*Schizophrenia.*—Various experimental approaches to the problem of schizophrenia have been reported during the past year [Huston & Senf (152); McGinnies & Adornetto (153); Doust (154)]. Kety's finding (69, 70) that oxygen consumption of the brain is 'normal in schizophrenia' is of interest. The question of histopathological changes in the testes of schizophrenics has been investigated by Blair and his co-workers (155).

*The electroencephalogram in psychological disorders.*—This is the title of a recent comprehensive review by Kennard (156) who has assembled and evaluated the evidence of many authors, published over a period of 15 years, on the subject of the EEG in psychological disorders. This was a much needed review, and the present status of this important area is clearly given in this valuable paper. There have been a number of very recent studies in this area [Darrow (157); Hill (158); Levy & Kennard (159); McAdam & McClatchey (160)].

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## HEARING

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This review covers the period from June, 1951 to June, 1953. The topic of hearing was reviewed two years ago by Gernandt (18a), who devoted the greatest amount of his attention to the end organ of hearing. Because of this, as well as the personal bias of the present author, major emphasis will here be placed on the central pathways concerned with audition. No attempt has been made to limit the papers reviewed to those which might fall within the most rigorous definition of physiology. Because the flavor of this review is so strongly neurological, this would not be practical because neurophysiology, neuroanatomy, and physiological psychology are by now inextricably involved with each other, and no reasonable lines can be drawn between them.

*End organ.*—There has been, during the review period, approximately the normal crop of articles on the cochlea, middle ear, etc. They fail to reveal any strong trend by virtue of coincidence of direction, but, instead, tend to be scattered over a rather wide area of structure and function. For the reasons stated in the introductory paragraph, the studies of the end organ are reviewed in almost no detail.

Engström & Wersäll (14) open a new approach to the structure of the organ of Corti based on electron microscopy. Hitherto unknown detail of structure of hair cells and accessory elements is demonstrated. It is too early to evaluate in terms of cochlear function, although, as we learn to digest this type of information, it should have considerable effect on our appreciation of cochlear activity. Hilding (28) presents new evidence on the normal relations of the traditionally elusive tectorial membrane and develops from it a theory of transmission of sound vibration to the hair cells. Bocca (6) reports a detailed study of cochlear innervation which revives the question of a dual system of nerve supply to the sensory epithelium.

Rüedi (47) describes systematic observations of morphological changes both in hair cells and other cochlear structures resulting from a variety of mechanical and chemical insults and derives from this a number of ideas as to details of cochlear functions. Kristensen (32) reports on acoustic and vestibular function in guinea pigs after removal of the membranous external semicircular canal.

Heise & Rosenblith (27) have studied the electrical responses to acoustic stimuli at the round window of the pigeon. They relate the components of the click response in the pigeon to microphonic and neural components of similar responses in mammals, and the characteristics of the response are compared to certain behavioral observations. Békésy (3) reports measurements of DC resting potentials inside the cochlea and raises several interesting questions as to possible relations of these to cochlear potentials produced



by sound stimuli. Wever & Lawrence (58) have devised a very ingenious and direct method of studying sound conduction in the cochlea by simultaneous stimulation via basal and apical routes with the same tone in such a way that intensity and phase relation between the two stimuli could be independently controlled, recording the response at the round window membrane. Their results lead them to reject a traveling wave principle in favor of a fluid principle of conduction, and, other factors being taken into account, they arrive at a theory of pitch perception involving both spatial and frequency cues—in short, the volley theory. Thomas (54) has written an essay in support of a theory of pitch discrimination that depends largely on the properties and movements of the "layers" or columns of fluid in the cochlea.

By refinement of methods previously used without conspicuous success, Schuknecht & Neff (50) have demonstrated hearing losses below 500 c.p.s. in cats, as a result of restricted damage to structures within the apical turn of the cochlea. Lindsay *et al.* (35) find that the endolymphatic sac and periotic duct can be obliterated with structural and functional impunity to the cochlea as shown by lack of histological change or loss of auditory acuity by functional test. Lawrence & Wever (33) report data on structural and functional effects on the organ of Corti resulting from oxygen deprivation of varying degree and produced by various methods.

Metz (36) presents observations on threshold of reflex contraction of the muscles of the middle ear and its relation to acoustic impedance and recruitment of loudness. Gill (21) describes the movements of drum and ossicles under stroboscopic light in response to high intensity sound stimuli of different frequency in cadavers and living rabbits. Hind (29) reports on electrophysiological determination of tonotopic organization in the auditory cortex of the cat, using the transient potential change in response to the onset of a pure tone.

Békésy (4), by use of a special perforating electrode which permitted him to record in detail from structures within the cochlea, was able to conclude that the organ of Corti plays an important role in the production of first order microphonics and that Reissner's membrane and the basilar membrane serve to isolate electrically the organ of Corti from the perilymph.

*Central auditory system.*—The period under review would be notable, if for no other reason, because from two different laboratories there have come reports of lasting effects on auditory function as a consequence of destruction of auditory cortex. A long list could be cited of previous failures in this direction or of successes limited to highly transient dysfunction of one kind or another. The current success in producing enduring functional deficits is the result of nothing more novel than determined effort to establish in animals learned auditory discrimination patterns of sufficient complexity to require the use of the best integrative capacity at the animal's command.

Meyer & Woolsey (38) trained cats to discriminate sounds (a) differing in frequency and (b) differing in intensity. After complete destruction of all

known auditory areas, including Somatic II, Auditory I and II, and the posterior ectosylvian gyrus, the animals were and remained unable to discriminate between tones of different frequency. Less inclusive lesions failed to impair frequency-discriminative ability. Intensity discrimination survived lesions which abolished frequency discrimination, as would be expected from the earlier studies of Raab & Ades (44). This is the first instance, to the best of the reviewer's knowledge, in which two analytical characteristics of hearing have been dissociated in experimental animals by lesions confined to auditory and immediately adjacent cortical areas.

Diamond & Neff (11) trained cats to respond differentially to a pair of tonal patterns containing the same component frequencies but in different sequential relation. After complete bilateral destruction of all cortex electrically responsive to auditory stimulation, the discrimination habit was lost and could not be relearned. Partial ablations of the critical areas resulted in loss of the tonal pattern discrimination if the lesions were large; however, relearning was possible in these cases. Small partial ablations failed to interfere with the learned habits. Jerison & Neff (30) obtained essentially similar results in monkeys.

Unlike the Meyer-Woolsey cats, those of Diamond & Neff were able postoperatively to learn discriminations based on simple change in frequency. No explanation of the apparent discrepancy is to be found in the evidence available. It might be pointed out, without in any way detracting from the importance of these three studies, that visually-guided discriminatory behavior in monkeys is much more sensitive to cortical insult if the animals are trained to one particular problem than if they have wide experience of many examples falling into a class of problems [Meyer, Harlow & Ades (37)].

Tunturi (56) has reported an analysis of electrical responses of strychninized patches along his previously described vertical bands of isofrequency contours in the middle ectosylvian cortex of the dog. He recorded response to varying intensity of sound, finding that contralateral stimulation gives uniform response curves along a given band, whereas with ipsilateral stimulation, the threshold increases as the recording electrode moved downward along the band.

Rosenzweig (46) found in cats that the electrical response of auditory cortex to clicks is greater to contralateral than to ipsilateral stimulation. When both ears were stimulated, the response was usually greater than that to contralateral alone but smaller than the algebraic addition of contra- and ipsilateral response. He concludes that in the auditory cortex of both hemispheres each ear is represented by a population of cortical units, that representing the contralateral ear being greater than that of the ipsilateral, and that some units are common to both populations.

Lilly (34) has shown, by recording cortical activity under an array of 25 electrodes, a picture of the spontaneous and evoked potential changes in the cat's auditory cortex which is much more comprehensive than anything that

can be recorded by more conventional techniques. For example, at deep levels of anesthesia, waves traveling over the auditory areas I and II are blocked as they spread to the posterior ectosylvian cortex; however, at successively lighter levels of anesthesia, this boundary, although sharp at deep levels, ceases to be an obstacle, and waves traverse it freely. He concludes that "the effect of anesthesia is to isolate functional regions from one another in the cortex, to simplify their activity, and to prevent interactions between contiguous regions."

Chow (8) has made estimates of the total number of neurons and the number of cells per unit volume in the auditory centers of the monkey. The ratios of the successively increasing cell populations in successively higher centers are expressed as an expanding cylinder. Chow speculates cautiously on the possible functional significance of the numerical relationships and contrasts these with the rather different ratios of other sensory systems.

*Frequency localization.*—An old problem, that of frequency localization, which for several years received little attention, has been revived in recent years, especially by the exploration of the auditory pathways by microelectrode techniques. The results have demonstrated the extreme oversimplicity of earlier views and have added greatly to the sophistication of our thinking along these lines, as well as to the sophistication of methodology. As might be expected, these studies have also increased the number and complexity of problems yet to be investigated.

An important and carefully executed series of microelectrode experiments by Galambos and several others (15, 17, 45) has demonstrated a complexity of response in the medial geniculate body of the cat scarcely suggested by earlier studies. The response of single elements to click stimulation indicates that each unit discharges at a fixed latency after stimulation and that latency of different units varies over the astonishingly wide extremes of 6 msec. and 125 msec. Various possible explanations of this phenomenon are discussed, and these have significance to neural theory far beyond their mere relevance to auditory function. The discussion further emphasizes the increasingly apparent need for thinking in terms of multiple neuronal pathways and temporal delay and inhibitory as well as excitatory activity at synapses. There is evidence that mechanisms for dispersing and "storing" neural excitation which are usually thought of as cortical flourish at sub-cortical levels as well.

The same group, with similar methods, found that, "Pure tones may evoke single unit responses from the medial geniculate, although a large number of units responsive to clicks or noise or both could not be excited by tones." Neither the rather wide band of frequencies which may excite a given unit, nor the lack of constancy of locus of units responding to a given frequency-band, seem to offer much support to the concept of a rigorously faithful point-to-point projection of cochlea to medial geniculate. Of special significance and interest are the observations on suppression of clicks by

pure tones, both delivered to the same ear, and the implications which cannot be detailed here.

In two studies, Thurlow *et al.* (55) and Gross & Thurlow (24) have reported experiments respectively on the inferior colliculus and the medial geniculate body of the cat, using microelectrode recording of the response from the inferior colliculus produced by continuous tones, onset of tones, clicks, and thermal noise. Both slow wave and spike responses occurred under various conditions of stimulation and recording. Details of latency, threshold, adaption, etc. were given. Some evidence is presented indicating correlation of position of response and frequency of stimulation, most of this being derived from observation of selective masking of click response by pure tone stimuli of different frequency. In the medial geniculate, these authors found that the response to tonal onset and click stimulation usually consisted of spike discharge. They describe elements giving response over narrow bands of frequencies and find further evidence of frequency specificity in the masking of clicks by pure tones in constant locations. Unlike Galambos and his co-workers Gross & Thurlow felt the evidence favored a frequency-specificity concept of auditory projection at this level.

Boyersky & Peacock (7) studied the cortical response in dogs to pure tones and complex stimuli. Their results led them to believe that there is widespread representation in the auditory cortex for pure tones as indicated by the "secondary" response, and would apparently oppose the concept of restricted area of response to stimuli of given frequency.

Perl & Casby (43) and Galambos & Perl (16) report results of recording response to clicks and pure tones from the auditory cortex of the cat, using the Laplacian electrode. Whereas, with monopolar recording, the click response can be detected all over auditory areas I and II, the Laplacian electrode records only from I. The meaning of this result is not clear. With pure tone stimulation, conventional monopolar recording yields some evidence for localization of frequency response, but the Laplacian array shows a response to a much narrower band at any given locus.

The foregoing studies seem to be somewhat at variance with each other, indicating that (a) the methodology is not equivalent, and (b) more work is called for which will exploit some of the techniques and problems which these have opened.

*Acoustic trauma.*—The interest in acoustic trauma, judging by the number of studies which have appeared since the last review of the subject by Gernandt, has abated not at all; in fact, it is apparently increasing. There is now, however, a trend away from blast injury and the experimental production of trauma by pure tones and toward the acute and cumulative effects of sustained or repeated exposure to high intensity noise such as that experienced by military personnel working around jet aircraft. Furthermore, whereas previous studies were concerned with noise-levels of 140 decibels or less, the problem is now intensified by the increasingly common

occurrence of human exposure to still higher levels, and one notes the more and more frequent mention of noise fields of 145 decibels, 150 decibels, or even greater. Each technical advance in the instrumentation of war now seems to push more closely the limit of human endurance. The bulk of the papers dealing with the effects of exposure to noise, aside from blast injury, group themselves into those dealing with (a) aircraft noise, (b) experimentally produced noise (i.e. special sirens, etc.), and (c) industrial noise. The first two of these will be reviewed more completely than the third since they contribute more to physiological knowledge, whereas the third leans towards medicolegal and personnel selection problems. It should be noted, however, that these latter problems are currently matters of increasing concern to large numbers of people.

Ruëdi & Furrer (48), studying the auditory effects of jet aircraft (Vampire) noise, gave particular attention to the characteristic whistling noise produced by the siren effect of the compressor, which is most noticeable at the front of the plane. The strongest component (30 db. above general noise level) is 850 c.p.s. Exposure to this sound for 2 min., sound pressure being 140 db., was enough to produce a threshold rise of 40 db. in the 600 to 1100 c.p.s. range with recovery in less than 24 hr. This is typical of other experiments. Audiograms of two mechanics who had had repeated exposure showed permanent loss having the same character as the temporary losses. Prolonged exposure of guinea-pigs produced variable histological changes in the inner ear which always began with degeneration of outer hair cells. It is noted that pilots are well protected from the most intense noise by cabin, helmet, etc., so that the main problem is that of mechanics. Ear defenders prevent the hearing losses noted above.

Senturia (49) tested hearing of flight trainees at various stages from pre-flight through basic and advanced training. These men were exposed to sound fields of 110 to 120 db. for protracted periods. Significant numbers showed elevation of threshold at one or more frequencies, most commonly 2048 to 5792 c.p.s., but these were temporary and recovery occurred after 24 hr. of freedom from noise.

Gallagher & Goodwin (18) find that brief exposure to white noise at 115 db. above threshold causes marked rise in threshold for the 2048 to 8192 c.p.s. range with return to normal threshold in 20 to 30 min.

Parrack & Eldredge (42) give a good summary of noise problems associated with aircraft maintenance from a practical standpoint. While it is not a study of hearing as such, anyone interested in noise problems having to do with jet aircraft will be interested in the careful and comprehensive analysis of the noise field of a turbo-jet engine by von Gierke and his co-workers (20). They have determined directional patterns and sound pressures within those patterns around such an engine at three representative power settings, and they discuss the physical origins of various components of the noise.

Alexander & Githler (1) studied the effect of exposure to jet-engine noise

(140 db. for a period of 15 min.) on cochlear potentials and histological structure of guinea pig ears 6 to 8 weeks after exposure. The group audiogram loss was 34 db. Primary damage to the cochlea was 6 to 12 mm. from the basal end and the authors thought the degeneration spread from the middle of the cochlea basalward more than toward the apex. Electrical sensitivity is depressed according to distribution of cochlear damage. They were impressed by the widely distributed destruction.

Dickson (12), discussing effects of intense sound and ultrasound on the ear, points out that intensity is a more important factor than frequency, that hearing loss may at first be gradual and reversible but with continued exposure becomes permanent, that ear defenders constitute good protection against hearing loss, and that there is no evidence of acoustic trauma from airborne ultrasonic sound.

Eldredge & Covell (13) have reported an excellent and extensive series of experiments in which 178 guinea-pigs were exposed to sounds derived from one of three different sources for varying times at various sound levels up to 165 db. Most of these animals' ears were examined histologically. This is probably the most exhaustive and significant study of its kind to date. It is impossible here to summarize adequately the variety of data afforded.

To illustrate that with increasing intensities of sound energy the effects of sound begin to pass out of the realm of audition, one may cite the study of von Gierke, Parrack & Eldredge (19) on the heating of animals to the point of death by high energy level air-borne sound. They analyze the absorption of sound of varying characteristics by the body and present a theoretical explanation for the phenomena observed.

The problem of industrial noise and its effects on man is the subject of an excellent review by Parrack (41). He reviews the physiological response mechanisms and presents criteria for evaluating noise, measured in octave bands, with respect to the probable response of man. Frequency characteristics get special attention, and materials used for noise control are evaluated in the light of their effectiveness as a function of frequency. In a second comprehensive review Parrack (40) deals with the history of the science of ultrasonics and its possible applications and hazards for biology, medicine, and industry. It includes a useful and timely glossary of terms, the definition of which have become somewhat elastic and, therefore, correspondingly confusing in general use.

Theilgaard (52) has presented an elaborate and interesting series of observations on effects of acute exposure to noise on workers who have been chronically exposed to industrial noise for varying periods of time. He describes subjective experience and objective measurements. Older workers with conduction loss showed very little effect of 5-min. exposure to 100 db. sound, whereas younger workers who had no conduction deafness showed the same subjective response as normal controls and exhibited transient dips in the audiogram. Theilgaard concludes that conduction deafness con-

stitutes a protection against effects of exposure to loud noise and the mean value of the effect of auditory fatigue is reduced with diminished hearing. Applications to problems of selection and protection of personnel who work in high noise levels are suggested.

Wheeler (59) reports well-controlled study of 78 shipyard employees followed from beginning of employment in high level noise fields (86 to 100 db.). More than half developed, over a period of time, hearing deficit of 15 db. or more at one or more frequencies. Goldner (23) evaluated occurrence and character of deafness in 600 shipyard workers. Walmer (57) briefly reviews the problem of noise in industry.

Effects of blast injuries to the ear and methods of treatment are reported by Karkis (31). Schuknecht, Neff & Perlman (51) have studied the auditory damage following blows to the head in cats. Both auditory testing (audiograms determined by conditioning method) and cochlear response were studied before death, and gross and microscopic examinations of skull, brain, and inner ear followed. While hearing losses sometimes occurred without demonstrable pathology, the 40 db. level of loss seems to be rather critical with respect to degree of damage of the organ of Corti. With loss of 40 db. or less, outer hair cells showed damage; losses greater than 40 db. usually were coincident with destruction of inner as well as outer hair cells. Effects in general were like those seen in blast or sustained exposure to loud noise. Alexander & Githler (2) report the effects on guinea-pigs of intense pure tone stimuli, the magnitude of the initial injury being controlled to the point of 60 db. loss in sensitivity to the stimulating tone. They find that injury by low tones is more extensive in terms of frequency range and more permanent than are injuries due to high tone exposure. They interpret their results as unfavorable to a place principle of cochlear function.

Davis, Parrack & Eldredge (10) find that air-borne ultrasonic vibrations do not constitute a hazard to sense organs or nervous system. High intensities, rather than high frequencies, are potentially hazardous. Sounds above 120 db. stimulate tactile end organs and may cause temporary or even permanent hearing loss. Levels above 140 db. are painful to the ear and are dangerous. They cite a case of ruptured drum in a subject during exposure to a tone of 6500 c.p.s. at 159 db., and there was a probably permanent high tone deficit. The authors comment on subjective feelings of fatigue, irritation, etc., induced by very intense sound as a warning of presence of stress which may become dangerous.

*Effects of drugs on hearing.*—While the theoretical significance of the well-known effects of streptomycin on hearing is as yet not very clear, it is probably not amiss to review some of the recent careful surveys of this problem because of the increasingly apparent advantage of one drug over another from the standpoint of disastrous side effects. Furthermore, there begins to be reason to believe the streptomycin derivatives could become



important experimental tools in audition because of the peculiar selectivity of the effects of the several variants.

Heck, Lynch & Graves (26) compared the toxicity of streptomycin and dihydro-streptomycin in a group of 68 patients, 34 receiving each drug in therapeutic dosage (1 gm. per day for 120 days) audiograms being taken prior to treatment and at intervals after 120 days of therapy up to six months. Vestibular function was examined by the Kobrak method. They reported only five cases with auditory disturbance, all having had dihydro-streptomycin, but noted that this was irreversible and progressive for the period studied. Six of the streptomycin group and two of the dihydro-streptomycin group had vestibular disturbance. These are among the mildest effects reported by anyone, but follow the usual pattern, i.e., dihydro-streptomycin neurotoxic effects are predominantly auditory, while streptomycin effects are vestibular.

Glorig (22) in similar studies, but with more variation in dose and duration of therapy, on a total of 211 patients found a somewhat more alarming degree of toxicity. He concludes that dihydro-streptomycin is significantly, not to say dangerously, toxic in doses of 2 to 3 gm. per day for three months or more. O'Connor, Christie & Kirby (39) reached similar conclusions on a smaller series of patients and point out further that streptomycin should be considered the drug of choice for a prolonged course of treatment, since compensation for impaired labyrinthine function is satisfactory, but hearing losses from dihydro-streptomycin are permanent, severe, and frequent.

Berg (5) reports experimental studies of site of lesion responsible for vestibular and auditory impairment after streptomycin treatment. He found that the sensory epithelium of cristae and ampullae was flattened, shrunken, and without cilia. He concluded that, although this would seem still open to question, the changes reported by others in Scarpa's ganglion and Deiter's nucleus are secondary to the changes in the sensory epithelium.

Thomas (53) describes in detail the vestibular dysfunction in 66 patients on streptomycin for varying periods and dosages. There were no hearing losses. Site of lesions in these was not determined, but Thomas notes that in experimental animals similarly treated histological changes could be found in the sensory epithelium of cristae and ampullae, Deiter's nucleus, and the medial longitudinal bundle.

In guinea-pigs, Christensen *et al.* (9) found the expected deterioration of hearing and vestibular function after fairly large doses of streptomycin, and this was paralleled by progressive degeneration of cochlear and vestibular nuclei. They also noted changes in other nuclei of the medulla, in the Purkinje cells of the cerebellum, and in motor cells of the cerebral cortex. Contrary to the observation noted above, Christensen found the labyrinthine sensory cells and the organ of Corti to be intact. Cochlear microphonics were not affected.

Hawkins & Lurie (25) in carefully controlled experiments treated cats with the equivalent of 100, 200, or 400 mg. doses of streptomycin per kg. of body weight for periods up to 60 days. Severe effects were noted in vestibular function and cochlear microphonic (click stimulation), and less severe but still profound effects on auditory cortical response. Degeneration of vestibular sensory epithelia and organ of Corti was demonstrated, the degree depending on dosage and length of time allowed for changes to take place. Of particular interest was the observation in some of the cochleae of complete absence of inner hair cells with intact outer hair cells. In cochlear degeneration due to other causes (e.g. acoustic trauma) the pattern is uniformly the reverse, i.e., intact inner hair cells, absent outer hair cells, or both absent. This may offer an approach to the specific functions of inner as compared with outer hair cells.

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## THE PITUITARY-ADRENAL SYSTEM<sup>1,2</sup>

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This paper is not intended as a summary in review of the past year's literature on pituitary-adrenal function. We wish primarily to present an essay on this subject discussing recent findings as they are relevant to the significant problems. An exhaustive presentation of the literature has therefore not been attempted.

What, then, are the major experimental problems in the field of pituitary adrenal relationships? In our opinion they are as follows: (a) the nature of adrenocorticotrophic hormone (ACTH), (b) the nature and control of the adrenal secretory product, (c) the basic physiological processes affected by adrenal hormones, (d) the role of the adrenal-pituitary system in stress, and (e) certain clinical-endocrinological problems relevant to pituitary-adrenal function.

### THE NATURE OF ADRENOCORTICOTROPHIC HORMONE

In his 1953 review Engle (1) stated: "The problem of the precise chemical nature of ACTH still eludes solution." This is also true today. A number of preparations have been made, each with obvious biological activity, and with equal obviousness differing from each other in chemical properties. The concept at one time advanced that ACTH is a protein hormone (molecular weight 20,000) containing as "prosthetic" groups active polypeptide moieties appears now to be untenable since the analyses of the electrophoretically pure Li-Sayers protein by electrodialysis, paper electrophoresis, and counter current distribution present clear evidence of inhomogeneity (2). Tyzlowitz (3) was the first to demonstrate activity in ultrafiltrates of pituitary extracts, but his finding was largely overlooked until the more detailed ultrafiltration studies of Morris and his associates (4). With the discovery of active material in peptic digests and acid hydrolysates of both swine and sheep pituitary protein the concept of ACTH as an active polypeptide, basic in nature, has gained status, and in fact polypeptide-like material having 200 to 400 times the activity of Li-Sayers protein has been described which is obtainable either from peptic digests subjected to counter-current distribution and puri-

<sup>1</sup> The survey of literature pertaining to this review was concluded June, 1953.

<sup>2</sup> The following abbreviations have been used in this chapter: ACTH (adrenocorticotrophic hormone); AA (adrenal ascorbic acid depletion); HL (hydrocortisone-like substance); DCA (desoxycorticosterone acetate); GFR (glomerular filtration rate); ACE (adrenal cortical extract); RPF (renal plasma flow); DOC (desoxycorticosterone); GH (growth hormone); DDD [1,1-dichloro-2,2-bis(*p*-chlorophenyl)-ethane]; DHIA (dehydroisoandrosterone); KS (ketosteroid); PMS (pregnant mare's serum gonadotrophin); F (17-hydroxycorticosterone, hydrocortisone); B (corticosterone); E (cortisone).

fication (5), or oxycellylose-adsorbates subjected to partition chromatography (6). Paper electrophoresis also effects a remarkable purification (7).

These highly active preparations have all been standardized by the adrenal ascorbic acid depletion (AA) method. Various preparations have high activity in this test but low activity in others and vice versa. The eosinopenic and AA properties of various polypeptide preparations show no correlation (8). Similarly AA<sup>2</sup> and adrenal weight-maintenance do not go hand in hand (2, 9). The therapeutic efficiency of various ACTH preparations apparently is not related to AA activity (10), and certain preparations administered to human subjects may have higher eosinopenic activity than others or may influence 17-ketosteroid excretion quite differently (11). An equine pituitary corticotrophin has been described (12) which has low AA activity but which appears to sensitize the rat adrenal to AA effects of other preparations. The concept of several ACTHs is advanced as a result of these observations. Against such a view is advanced evidence that the mode of administration, involving especially rates of absorption markedly affects the result observed. Thus Renold *et al.* (13) have found that ACTH when given by slow intravenous infusion to man will markedly stimulate 17-ketosteroid excretion and eosinopenia, but very rapid infusion (total dose in 30 sec. compared to several hr. by slow infusion) causes no detectable change in the two response measures employed. Similar dependence of the eosinopenic effect in man on rate of intravenous administration has been reported by Cope *et al.* (14). Renold *et al.* (13) also note that subjects resistant to intramuscularly administered ACTH respond significantly to the same preparation given intravenously. Bates (15) has observed similar disparities between intravenous and intramuscular ACTH in animals. Thompson & Fisher (16), comparing three methods of assay (AA, adrenal weight, and thymus involution tests) in rats, find also that the mode of administration may affect the ratios of response, *e.g.* gelatin in the medium appears to enhance certain responses differentially. Although Dixon *et al.* (9) give evidence of chemical separation of AA from the adrenal weight-maintaining effect and Reinhardt *et al.* (17) have separated the melanophore-expanding effect from AA in sheep ACTH preparations, Winter and his collaborators (18) have observed all three activities highly concentrated in polypeptide (5) from pig pituitaries which is definitively homogeneous by counter-current distribution criteria and which has extremely high AA activity (300 I.U. per mg.). These slightly puzzled reviewers suggest that until the chemical nature of the ACTH of various species is definitive, disagreement will continue.

Furthermore, all present measures of ACTH activity are indirect ones. They measure, in various species, what happens to processes one or several degrees removed from the primary effect of ACTH, namely, the stimulation of corticosteroid secretion. It has been shown (19) that corticosteroid production by the isolated bovine adrenal perfused with an ACTH preparation is roughly proportional to AA, and an assay of ACTH based on its corti-

costeroidogenic effect on the rat adrenals *in vitro* has been proposed (20, 21), but neither of these methods has been used for the intensive study of allegedly "pure" ACTH. Consider the hazards involved in any widely used ACTH assay: An aqueous solution is injected either subcutaneously, or intramuscularly, or intravenously, or even intranasally, and by any of these routes it meets with the chance of enzymatic destruction (13, 22, 23, 24); the ACTH reaches the adrenal and stimulates the production of corticosteroid, which may be chemically quite different in different species, and this corticosteroid then acts on a target organ, e.g. the thymus, melanophores, the changes in which are measured. The corticosteroid may be principally corticosterone in the rat (25), chiefly hydrocortisone but also corticosterone in man (*vide infra*), and we know not what in the frog. Again into rat, man, and the frog are injected extracts of swine, sheep, or beef pituitaries. Ideally we should know just what amounts of what corticosteroids ACTH produces as a result of its action on the adrenal of a given assay species. This would be the true measure of its activity; the correlations of this corticosteroidogenic effect with the numerous others studied should then afford a rational basis for diversity or similitude of ACTHs.

#### THE NATURE AND CONTROL OF THE ADRENAL CORTEX SECRETORY PRODUCT

This subject has been most recently reviewed by Verzár (26), Staudinger (27), and Pincus (28). The determination of just what steroids are secreted by the adrenal cortex is as yet incomplete. Fortunately the tools for such determination have been provided by the development of quantitative micro-methods for the extraction, isolation, and identification of steroids (29, 30, 31). The most direct data have come from the examination of adrenal vein blood of various species and from the analysis of the effluent from isolated perfused glands. The substances thus far identified in adrenal vein blood have been summarized by Pincus (28) and Bush (32). In the dog, ox, cat, ferret, monkey, and sheep both hydrocortisone (F) and corticosterone(B) are found, but the ratio F/B varies from 1 (ox) to 20 (monkey)<sup>3</sup>; in the adrenal vein blood of the rat and the rabbit B<sup>2</sup> but no F<sup>2</sup> have been identified. In addition to these two principal, and most easily identified, corticosteroids, other substances have been observed in varying amount. These are; (a) rather highly polar compounds, designated as "amorphous fraction" components (dog, cat, sheep), (b) 11-dehydrocorticosterone [rat, dog (cf. 33), cat] and cortisone [dog (cf. 33), cat, sheep], and (c) 19-carbon steroids, probably 11-hydroxylated [cat, rat sheep, and ox (33)]. There is thus evidence for the presence in adrenal vein blood of various species of some 7 to 10 steroids. Farrell (34), in a detailed study of dog adrenal vein blood, has re-

<sup>3</sup> Romanoff, Hudson & Pincus [*J. Clin. Endocrinol.* (In press)] find a similar high ratio in adrenal vein blood of human subjects receiving ACTH.



ported the presence of F, B, and 11-desoxycortisone, along with approximately 10 additional substances. Since Hechter *et al.* (35) have identified, following ACTH stimulation, 15  $\alpha$ -ketols in the effluent of isolated perfused cow adrenal glands and Bloch *et al.* (cf. 28) have found at least two 17-ketosteroids, it has been suggested (28) that either the isolated perfused gland allows the escape of substances ordinarily retained in the gland *in vivo* or that available micromethods do not allow the detection of minor quantities of corticosteroids in the small amounts of adrenal vein blood ordinarily available for analysis. That minor amounts of biologically extremely potent substances may be extremely significant is attested by the finding in monkey adrenal vein blood, as well as in perfusates of the monkey gland, of a salt-retaining steroid (36) at least 25 times as active as 11-desoxycortisone (37).

The mechanism whereby steroidogenesis is accomplished in the adrenal cortex has been discussed by Hechter (19), Vogt (38), and Pincus (28). Although Hechter suggests that the decline in steroid output with time in isolated perfused glands indicates that ACTH is essential for corticosteroidogenesis, Vogt presents data demonstrating (a) that at least over a few hr. the biological activity of dog adrenal vein blood *in vivo* or from perfused adrenals *in vitro* is essentially identical and (b) that the blood of a dog hypophysectomized for one month will, on perfusion, sustain the same degree of cortin output. It is agreed, however, that ACTH markedly stimulates corticosteroid release both *in vivo* and *in vitro*. Bush's studies of adrenal vein blood in various species (32) suggest furthermore that ACTH merely increases quantitatively the amounts of the characteristic substances present. The implication is that ACTH acts on a common precursor (or precursors) of the final secretory product to make it available for corticosteroidogenesis. In acute experiments this common precursor is probably cholesterol, but just how ACTH makes it available for the series of enzymatic transformations leading to characteristic corticosteroid is still speculative (19, 28).

Less direct methods for the determination of the nature of the adrenal secretory product involve the measurement of steroids in peripheral blood and in urine. Since metabolic transformations of secreted corticosteroid take place in various tissues of the body one can only deduce from the steroid patterns of blood and urine what the true secretory substance may be. Thus Done *et al.* (39) find species differences in peripheral blood hydrocortisone concentrations that correlate rather well with studies of adrenal vein blood (e.g. none in the rabbit, 2  $\mu$ g. per cent in the rat, 33  $\mu$ g. per cent in guinea pigs and 10  $\mu$ g. per cent in humans). Furthermore a brief increase in hydrocortisone-like substance (HL) in human blood follows ACTH administration (40), and HL<sup>2</sup> disappears in human blood following adrenalectomy and cortisone withdrawal (41). In a case of Cushing's syndrome and in a patient with breast carcinoma markedly elevated blood levels of F and B are found,

and the 2 to 1 ratio of F/B seen in normal human peripheral blood is increased somewhat in the patients (42). However, a detailed study of blood corticosteroids in any species is notably lacking.

Urinary corticosteroid studies give evidence of the nature of adrenocortical secretion on the basis of the types and amounts of substances clearly deriving from adrenal precursors. Since  $\alpha$ -ketolic steroids, 17-hydroxylated-21-carbon steroids, and 11-oxygenated-19- or 21-carbon steroids are characteristic adrenal substances, their presence (or absence) in the urine under various conditions has been sought. The purely technical problem of adequate extraction and identification of urinary corticosteroids has largely overwhelmed attempts at systematic survey. It is now clear that the extraction under mildly acidic conditions previously practised is inadequate for full recovery of urinary corticosteroid. Numerous observers are agreed that hydrolysis with  $\beta$ -glucuronidase gives much larger yields of  $\alpha$ -ketols and 17-hydroxy  $\alpha$ -ketols (29, 43, 44). An array of corticosteroid-like substances is found when enzyme hydrolysates of human urine are subjected to fractionation on paper (45), and this array is still found (with some alteration) following adrenalectomy and replacement therapy with cortisone or by hydrocortisone (46). Since the administration of hydrocortisone (46) and cortisone (46, 47) to either adrenalectomized, Addisonian, or normal subjects leads to the excretion of both Compounds E<sup>2</sup> and F<sup>2</sup> and their ring A reduction products, it is evident that Compounds E and F are intraconvertible in the body. Since administered cortisone in man appears to be metabolized to 5 $\beta$  pregnane (or etiocholanone) transformation products almost exclusively and with no removal of the 11-oxygen function (48), it is hopeful that studies of these types of metabolites in the urine may give a good approximation to the secretion of 11-oxygenated corticosteroid. Fortunately fairly usable methods for the separation and quantitation of the 11-oxygenated-17-ketosteroids are available (30, 49, 50).

All considerations of corticosteroidogenesis return to the problem of enzymatic transformations in the adrenal cortex. The potency of adrenal tissue for several characteristic reactions has been investigated. An 11 $\beta$ -hydroxylase has been characterized (51) which acts on both C-19 and C-21 11-desoxy steroids. Furthermore, 17 $\alpha$ -hydroxylation and 21-hydroxylation of 17- and 21-desoxy C-21 steroids have been demonstrated in adrenal homogenates (52, 53) and in aqueous solutions from adrenal breis (54). Indeed a direct action of ACTH upon adrenal slices causing a facilitation of corticosteroidogenesis (20) and promoting the incorporation of radioacetate into hydrocortisone (21) has been demonstrated, and methods for the characterization of steroids arising from such preparations are readily available (30, 55). The study of the factors involved in these enzyme systems, the effects upon them of numerous experimental variables applied both *in vivo* and *in vitro* offer a fruitful field for investigation.

THE BASIC PHYSIOLOGICAL PROCESSES  
AFFECTED BY ADRENAL HORMONES

*Protein.*—Two major aspects of protein metabolism which have engaged the interest of adrenal physiologists are (a) anti-anabolic and (b) catabolic processes. Closely related to these are the influences of adrenal cortical hormones on tissue responses and growth processes.

Roberts (56) has reviewed the aspects of the catabolic processes enhanced by adrenal cortical hormones and has presented further evidence indicating protein mobilization from spleen and liver with adrenal cortical extract. With the use of  $C^{14}$ -amino acids, Clark (57) has shown a definite anti-anabolic effect of cortisone. He found that animals receiving the amino acids in conjunction with Compound F excreted more of the isotopic compounds in the urine. Adrenalectomized animals incorporated more amino acid into the tissues and excreted less isotopic amino acid than normals. Although Compound F has a small effect on the respiration of lymphatic cells, it definitely inhibits the rate of incorporation of  $C^{14}$ -amino acids into the protein of the cells (58). A higher concentration of Compound F was required to inhibit amino acid incorporation in lymphosarcoma. Attesting to the inhibition of cellular processes by adrenal cortical hormones is the report that ACTH injections inhibit the turnover rate of  $P^{32}$ ; the results were interpreted as reflective of the inhibition of mitosis of lymphocytes, which were the cells studied (59). The antimitotic effects of adrenal steroids have been reported on other tissues such as the epidermis (60) and *Arbacia* eggs (61).

There was found an increase in the total fat content of livers of rats as well as enlargement of the liver after cortisone treatment. The increase of liver size was the result of the laying down of cytoplasm (increase of ribonucleic acid) without the formation of new cells (desoxyribonucleic acid was not increased) (62). The livers of guinea pigs were also increased in size after cortisone (63) and there was an increase in the susceptibility of rat livers to chronic damage by  $CCl_4$  as shown by the bromsulphalein retention test (64).

Cortisone-treated chick embryos showed a marked inhibition of growth which was evident primarily in the protein and ribonucleic acid content, but not in the desoxyribonucleic acid, when expressed in terms of the unit weight of the embryo (65). When rats were given 1 mg. daily doses of ACTH for eight days, the methylation of homocysteine in liver slices was unaffected but there was a decrease in nicotinamide and an increase in guanidoacetic acid methylation. Formation of tyrosine from phenylalanine and uric acid from xanthine was inhibited (66).

Higher and more prolonged levels of amino acid were found in Addisonian patients after the infusion of amino acids (67). Since there is a reported increased conversion of amino acids to urea in Cushing's syndrome this finding is interpreted to be a demonstration of defective amino acid catabolism. Increases in the excretion of amino acids were also reported after ACTH (68).

Differences were observed in the nitrogen metabolism of elderly patients receiving ACTH or cortisone between the acute and chronic phase of medication. Both compounds caused increased nitrogen output in the first few days. However, with continued administration there was a return to a positive nitrogen balance with the appearance of some edema and water retention. Initially both compounds gave a feeling of well being, but after cessation of treatment there was observed some irritability and mental depression (69).

In contrast to the studies indicating decreased amino acid incorporation into tissues after the administration of adrenal cortical hormones is the report that  $S^{35}$ -cysteine incorporation into protein was increased after ACTH. Hypophysectomized and adrenalectomized rats showed a decrease. Not only cortisone but desoxycorticosterone acetate was effective in restoring this rate back to normal. This study indicates that all amino acids do not respond in the same manner to adrenal steroids with respect to anabolic processes and that DCA<sup>2</sup> is effective in protein metabolism (70). Although a decrease was observed in the sulfhydryl level of the blood after x-radiation, it is apparent that this is not mediated through the adrenal-pituitary system since adrenal cortical hormones do not reproduce the effect (71). However, ACTH does induce a transitory drop in the sulfhydryl level of the blood when measured by a modified amperometric technique (72). A single small dose of ACTH was found to increase the nonprotein sulfhydryl level of the rat adrenal (73). This coincides in time with the decrease in the blood levels previously reported (72).

*Antiphlogistic and tissue effects.*—Based on the measurement of antifibrinolysin and its relation to inflammation, a hypothesis of hormonal balance in the control of inflammation is presented. Growth hormone and thyroid cause a decrease in antifibrinolysin titer which is related to increased inflammation, while ACTH and cortisone increase the antifibrinolysin content and decrease the inflammatory processes. A swelling index was used as a measure of inflammation (74). The granuloma pouch technique (75) and the reaction to egg white (76) in rats have been used to test antiphlogistic effects of steroids. This effect requires an  $\alpha$ ,  $\beta$ -unsaturation of ring A and hydroxy groups at C-11 and C-17.

Both ACTH and cortisone suppress normal cleavage of *Arbacia punctilata* ova when added directly to the medium. This inhibition is seen with sperm as well. Testosterone and somatotropin have no effect on eggs or sperm. The cleavage of the egg when it occurs is abnormal. It is presumed that this is effected by direct action on cellular activity (61).

The guinea pig is quite resistive to the protective effect of cortisone in anaphylactic shock (77). This was also shown with regard to protection against 2-4 dinitrochlorobenzene (78).

When cortisone is given in experimental brucellosis, a mild infection in the liver becomes fulminating (79). In chronic infection, cortisone has no

effect. The use of cortisone in one patient apparently was effective, but the culture was still positive. It is cautioned that cortisone should be used only in very ill, toxic patients, and then only with an adequate regime of antibiotics (80). Adrenal cortical overdosage does not inhibit bacterial removal from the splanchnic viscera (81). The *in vitro* effects of cortisone on chick embryo chorioallantoic membrane tissues results in significantly greater final concentration of influenza B virus than observed in normals. This is probably due to the greater survival of membrane tissues with the added cortisone (82).

The inhibition of granulation by cortisone is counteracted in part by DCA and completely by growth hormone (83). Massive doses of cortisone produce necrosis of mouse mammary carcinoma, but the inflammatory lesions which occur in the lungs, liver, and kidney are fatal (84). Cortisone induces metastases in adrenal carcinoma (85). Orchiectomy of new born mice of strain A causes a slight increase in the incidence of leukemia. The transplanting of adrenal glands doubles the incidence, and transplanting of pituitaries increases the incidence fourfold (86).

With continued injections of ACTH, no antibody formation against ACTH was measurable (87), and, furthermore, the antibody response to ACTH in acute hepatitis or in Rh-immunized women was negative (88, 89). ACE<sup>2</sup> inhibits the hair growth of young rats much less than that of adults (90). There is acceleration of hair growth after adrenalectomy in thyroidectomized rats (91).

It is obvious from the foregoing that the clearly demonstrable anti-phlogistic effects of corticosteroids are not susceptible of a single, unifying explanation. Activity at a cellular level is involved, but whether an aspect of nucleoprotein synthesis, antibody formation, fibrinolysis, or some more fundamental mechanism governs the diverse reactivities observed is yet to be demonstrated.

*Electrolyte metabolism.*—Since the effect of adrenal cortical hormones on electrolytes is concerned in great measure with kidney function, it is fortunate that adrenal physiologists and kidney physiologists have worked together toward understanding the mechanism of action of adrenal steroids. It is suggested that the major effects of adrenal cortical hormone on the glomerular filtration rate (GFR) and renal plasma flow (RPF) are not primary but secondary to their effects on the volume and composition of body fluids (92). If the blood volume and composition are normal, the hormones have no effect on the GFR<sup>2</sup> and RPF<sup>2</sup>. Inadequacy of renal tubular absorption of salt is the most clear-cut renal dysfunction in adrenal insufficiency (92). The resorption deficiency is only 2 per cent, but this small decrease extended in time is sufficient to cause large losses of salt through the urine. The location of this dysfunction is apparently at the distal end of the renal tubules.

In the adrenalectomized rat the reduced sodium store is accompanied by acidosis. The retention of potassium is related to higher pH in the urine.

DCA remedies these defects (92, 93, 94). Beta-hypophamine (Pitressin) counteracts some 80 per cent of the sodium loss of the adrenalectomized animal. The kidney is apparently not completely controlling in the electrolyte exchange, since potassium excretion does not account for the serum decrease observed after hormone administration (92).

Differences of action in the kidneys of various species such as the dog, rat, and man are emphasized. The factor of GFR should never be overlooked. ACTH, cortisone, and DCA cause an increase in the blood flow through the kidney. It is explained that renal arteriolar dilatation occurs with a constant arteriolar pressure: Thus a direct kidney action is postulated for the increase in GFR and RPF by the action of adrenal steroids on renal arteries. (95)

Cortisone depresses the renal tubular reabsorption capacity for phosphates whereas DOC<sup>2</sup> is ineffective (96). The phosphate load in itself does not influence the potassium and titratable acid excretion rates. Hypophysectomized dogs excrete a salt load at the same rate as normals (97), and the adrenalectomized dog is more sensitive to the salt-retaining action of DCA than is the normal dog. When the adrenalectomized mouse receives 0.5 mg. NaCl per gm. of body weight, DOC in small doses promotes sodium excretion. Retention of sodium occurs with larger doses of DOC (98).

In the study of water distribution after ACTH in man by antipyrine, T-1824, and bromide techniques, there was found a marked increase in body water (99). Where edema occurred, the extracellular compartment was large. Where no edema occurred, there was an increase in the intracellular compartment. However, the responses were variable. In the dog, doses of 50 to 300 mg. of cortisone per day for 4 to 14 days caused a diabetes insipidus-like syndrome (100). In the adrenalectomized dog the same symptoms were produced with 10 mg. per kg. of cortisone per day and beta-hypophamine (Pitressin) controlled the diuresis (101). However in a study of a patient with neurohypophyseal insufficiency where the anterior pituitary was definitely involved thyroxin, DCA, desoxycorticosterone glucoside, cortisone, ACTH, and growth hormone were all unable to concentrate urine when the water load was kept constant. Moreover, cortisone did not diminish the antidiuretic effect of posterior pituitary extract (Pituitrin) (102).

Although adrenalectomized dogs on 0.95 mg. per kg. of cortisone per day seem active and symptom-free, there occurs a slow accumulation of potassium which is verified through the electrocardiogram (103, 104, 105). When the dose is doubled the electrolyte picture is corrected. With low doses of cortisone, the hemoconcentration may increase, thus masking the true electrolyte condition in the blood. With low sodium intake, the minimum dose is 1.86 mg. per kg. per day. The electrolyte response depends both upon the dosage and duration of medication. In the rabbit 4.0 mg. a day for a week results in an increase in the pH and a decrease in the concentration of plasma



sodium. With continuation into the second week there is both a potassium and sodium retention with overhydration of tissues. Cessation of medication results in a prompt loss of weight accompanied by diuresis and a negative sodium balance. With a 25 mg. dose there is marked potassium excretion even though the animal does not eat well (106). No changes in fecal electrolytes were observed with ACTH or cortisone therapy (107).

Both nitrogen and electrolyte-retaining effects are observed when growth hormone (GH) is given to normal and adrenalectomized rats (108). It is postulated that there is a direct effect by GH<sup>2</sup> on the tissues and cells of the renal tubes. There are no differences in the response to DCA by rats on normal or protein-deficient diets (109). In the study of the influence of potassium on the electrolyte picture with high doses of ACTH, it was found that 360 m.eq. per day of potassium acetate with 100 I.U. of ACTH prevented sodium retention, and upon withdrawal of the hormone the sodium diuresis which occurs normally was not present (110).

*Carbohydrate metabolism.*—In examining the role of the pituitary and adrenal cortex in insulin sensitivity, it was found that it took larger than normal doses of ACTH and cortisone to abolish the increased insulin sensitivity found in hypophysectomized rats (111). Furthermore, in comparing the hypophysectomized rat with the adrenalectomized rat, it was clear that the removal of the pituitary resulted in greater insulin sensitivity than did the removal of the adrenal. These findings are interpreted to indicate that there is a pituitary factor separate from ACTH which is concerned with insulin hypersensitivity (112, 113). Growth hormone and adrenal steroids cause diabetes in the rat, but interestingly enough when both are given together there is no appearance of diabetic symptoms. It is thus evident that the combined effects of two diabetogenic hormones are neither additive nor synergistic, but antagonistic (114). Growth hormone and luteotropin (prolactin) can produce hyperglycemia and increased insulin sensitivity in the hypophysectomized rat, indicating that the adrenals are not necessary to the production of diabetes (115). A comparison of the actions of growth hormone and ACTH on various organs and tissues has been reported (116).

When cortisone and 17-hydroxycorticosterone (hydrocortisone) are compared by the continuous injection method in the rat there is an increase in urinary nitrogen and sugar, and atrophy of the thymus and the adrenals along with body weight loss (117). Hydrocortisone is twice as effective as cortisone by this route of administration. Though it is agreed that there is decreased hepatic gluconeogenesis in the adrenalectomized rat, there is still disagreement as to the utilization of glucose by peripheral tissues in this type of animal. Contrary to early interpretations, data are presented which favor the point of view that there is decreased utilization in the adrenalectomized rat and increased utilization in animals receiving cortisone (118). It is, however, agreed that the main metabolic effect of adrenal cortical steroids is gluconeogenesis from protein and fat.



Cortisone apparently inhibits phosphorylase activity, since the breakdown of glycogen is more strongly inhibited than its storage (119). When cortisone and diethylstilbestrol are given together the diabetic effect of each is additive or possibly synergistic (120); a dose of each too small to produce hyperglycemia in itself when given together produced hyperglycemia. Glycosuria was produced in partially pancreatectomized rats with both progesterone and 11-keto progesterone. The latter was the more strongly diabetogenic substance (121). This diabetogenic effect of 11-keto progesterone is manifest with or without the adrenals. There is a suppression of glycosuria when large doses of acetylsalicylic acid (Aspirin) are given to force-fed depancreatized rats (122, 123). This would seem to be contrary to the expectation that acetylsalicylic acid may act as a stimulator of the adrenal-pituitary system.

Glycogen formation from sulfur-containing amino acids such as serine, cystine, and glutathione is not evident in fasted normal rats. However, serine and cystine do contribute somewhat to glycogen formation in the adrenalectomized rat (124).

Rats treated with 50 mg. per day of DDD<sup>a</sup> for five weeks show atrophy of the inner layers of the adrenal cortex. Histological examination of the gland showed that the zona glomerulosa and medullary tissues were uninjured. Although these animals were sensitive to insulin, they reacted to potassium tolerance tests with no ill effects. These results support the view that the zona glomerulosa secretes electrolyte hormones while the zona fasciculata produces carbohydrate-effective steroids. These DDD-treated animals can be made diabetic with alloxan (125).

It should be noted that many of the contrasts in the foregoing data may be reconciled if Ingle's notion of the permissive action of corticosteroids is applied. An experimental animal prepared so as to allow the demonstration of permissive action, e.g., an adrenalectomized dog or rat, may, therefore, not be "controlled" by a "normal," e.g., nonadrenalectomized one.

*Vitamins.*—The vitamins appear to be involved both with corticosteroidogenesis at the adrenal level and with the effects of corticosteroid on end-organs. At times these two effects may be confused. Both pantothenic acid and ascorbic acid have been implicated in corticosteroidogenesis. The role of these and other vitamins in corticosteroid-affected metabolic phenomena is less obvious.

It is suggested that the intracellular situation brought about by pantothenic acid, biotin, or ascorbic acid is responsible for the increased survival of young adrenalectomized animals (126). Pantothenic acid deficiency depressed the synthesis of cholesterol in the adrenal after stress. Although there occurred a decrease in the cholesterol content of the adrenals after stress, it took seven days for the value to return to normal whereas only 24 hr. is needed in the non-deficient rat (127). Pantothenic acid deficient rats, when studied over a 90-day period, showed a steady decline in the cholesterol con-

tent of the adrenal but no changes in the ascorbic acid values. There occurred an increase in the succinic dehydrogenase content up to the fiftieth day, followed by a steady decline. No differences from normal in the ascorbic acid decrease following ACTH occurred in pantothenic acid deficient rats. These findings were only true with pantothenic acid deficient animals and not in animals deficient in other members of the B complex (128).

Cortisone had no influence on the metabolism of B vitamins. There was no influence on pyridoxine excretion or on the survival time of pyridoxine-deficient rats, no effect on riboflavin excretion or on the riboflavin content of the liver. No changes were observed in the pantothenic acid content of the tissues (129).

The scorbutic guinea pig excretes 5 times the normal amount of formaldehydrogenic substances in the urine. It is concluded that ascorbic acid is not needed for the adrenals to elaborate corticosteroids (130). On the other hand, the scorbutic guinea pig excretes reduced amounts of 17-ketosteroids. Added to this is the electrolyte picture which indicates that the scorbutic guinea pig is in a state of hypoadrenalism (131). The interpretation of these data is difficult unless one assumes that the steroids contributing to the formaldehydrogenic titre are inactive, at least for certain hormonal effects. With the administration of ascorbic acid to normal rats there was produced a transitory depression in the excretion of reducing lipids (132). Four weeks of treatment with L-cysteine produced a depression of both 17-ketosteroids and neutral reducing lipids which was reversed when ascorbic acid was given (132). On the other hand, ascorbic acid administration prevented the normally occurring rise in 17-ketosteroids following cortisone, but enhanced the excretion of corticoids. It was presumed that ascorbic acid prevented the metabolism of cortisone to 17-ketosteroids (133). When 4 gm. of ascorbic acid is given orally for four days to man, there is an increase in the corticoid excretion and a decrease in 17-ketosteroids. These results seem to be consistent both in the human and the rat. However, in the latter case the interpretation presented is quite different. It is presumed that ascorbic acid acts directly on the adrenal cortex (134).

Since the administration of ascorbic acid results in increased resistance to insulin (135) and a prolongation of the eosinopenia after cortisone (136), it is claimed that ascorbic acid acts synergistically with cortisone. However, the administration of ascorbic acid to children showed irregular patterns in the excretion of 17-ketosteroids and corticoids (137), thus indicating that this problem is not totally solved.

#### CLINICAL-ENDOCRINOLOGICAL PROBLEMS

Cortisone decreases the estrogen and androgen excretion in adrenal hyperplasia as differentiated from adrenal tumors (138). In hyperplasia the administration of ACTH increases estrogen and androgen (as 17-ketosteroids) excretion, but with no significant increase in corticoids (139, 140, 141). The

lack of corticosteroid output is confirmed by the finding that the blood 17-hydroxycorticosteroids do not increase with ACTH (142). Differential diagnosis of adrenal cortical dysfunction is suggested: (a) in congenital adrenal hyperplasia, a high 17-ketosteroid with normal or slightly increased dehydroisoandrosterone (DHIA) which decreases with cortisone; (b) in virilizing adrenal cortical tumors, a high 17-ketosteroid (KS) and a high DHIA<sup>2</sup> which is unaffected by cortisone; (c) in Cushing's syndrome, usually no elevation in 17-KS, but when present it is unaffected by cortisone administration (139). Gynecomastia was observed in adrenal tumor cases when a high estrogen output was not matched with a high 17-KS<sup>1</sup> (143). In the adrenogenital syndrome where a high 17-KS is present, the DHIA need not be elevated. Six cases were studied with Dingemans chromatography and only one case had a high DHIA. There was a fairly high 11-dehydroandrosterone fraction in these studies (144).

The clinical efficacy of cortisone in the adrenogenital syndrome is confirmed by several investigators (145 to 148). The preferred dose of cortisone is about 50 mg. orally per day. Good clinical response is accompanied by a decrease in 17-KS, but at times an intermittent hypokalemia results under this regime (147). ACTH was detected in the blood of children with congenital hyperplasia of the adrenal, while results were negative when no endocrine disease was present (149). The frequent finding of positive DHIA in premature children should not be confused with cases of adrenal tumors (150).

The hypertension present in congenital adrenal hyperplasia has been alleviated with cortisone. The decrease in the blood pressure is accompanied by decrease in the urinary 17-KS. At autopsy, one of the cases showed a marked hyperplasia of the zona glomerulosa (148). This finding again brings up the question of the differential production of steroids by the various zones in the adrenal cortex.

Chorionic gonadotrophin administration to two female castrates and one male with atrophic testes resulted in a rise in the 17-KS output as well as an increase in estrogens. These results suggest the stimulation of the adrenal cortex by the gonadotrophin (151). ACTH inhibits follicle maturation in the ovary and consequently uterine development. This is in agreement with the finding of increase in PMS<sup>2</sup> after adrenalectomy. ACTH induced an increase in PMS in the luteal phase. This may be an explanation for the reports indicating an increased titre of gonadotrophin in the urine after ACTH or cortisone (152).

The findings indicating that testosterone and methylandrostenediol do antagonize the cortisone atrophy of the adrenal (153, 154) have prompted their use clinically (155). There is much promise in the use of a nonvirilizing steroid with moderate anabolic effect which would prevent the depression of the adrenal cortex in cortisone therapy.

The increased level of  $\beta$ -17-ketosteroids found in schizophrenics suggests

a disturbance in the steroidogenesis of the adrenal cortex (156). No relationships were found between cerebral blood flow and changes in mental picture after ACTH or cortisone (157).

*Hypertension.*—The hypertension produced in young rats by implanting 20 mg. of DCA pellets continues after the disappearance of the pellets. This post-DCA hypertension is not mediated through the adrenal, thyroid, parathyroids, or gonads, but the pituitary is necessary. Apparently the central nervous system is the final pathway. The hypertension is unaffected by Na or K, but the kidneys are necessary. This hypertension, which resembles the syndrome in man, does not involve the adrenal cortex (158). In the study of the role of the pituitary in this experimental preparation, it was found that if hypophysectomy is performed prior to the implantation of the DCA pellets, there is no reduction of the polydipsia, but no hypertension is produced. The high fluid intake that is pronounced after DCA implantation is unaffected by hypophysectomy in the post-DCA preparation, but the hypertension is alleviated. The administration of cortisone and ACTH to the post-DCA hypophysectomized rat has no effect. The polydipsia and the hypertension are dissociated and the glucocorticoids have no influence (159).

Compound F has been found to be a more potent hypertensive agent than DCA (160). Aqueous solutions of beta-hypophamine with sodium excreting effect relieve the hypertension of DCA. This opposition of DCA could be elicited in the bilaterally adrenalectomized animal, and also occurred even when beta-hypophamine was given after the DCA hypertension was well established (161).

Inhibition of the development of DCA hypertension by a new steroid U-C16C (2, 21-diacetoxy-5, 7, 9-pregnatrien-20-one maleic anhydride adduct) was reported. Since no adrenal hypertrophy or thymic atrophy was present, it is considered that the action was not due to the stimulation of 11-oxycorticosteroid production (162).

In experimental renal hypertension, it is shown that even 87 to 99 per cent of adrenal cortical tissue is removed blood pressure is not lowered. Total removal, however, promptly reduces the blood pressure (163). Crude anterior pituitary extracts reduce the blood pressure of hypertensive dogs. Repeated injections are better than single ones. In all probability it is not the ACTH content of these extracts which may be the responsible agent (164). Hypertension induced in rats by NaCl and DCA does not interfere with conception, implantation, or normal delivery (165). Although blood pressure does decrease during pregnancy in renal hypertension there was in these DCA-hypertensive rats a failure of the blood pressure to drop, suggesting a difference in the chemical mediation of these two forms of hypertension (165). In the production of renal hypertension after wrapping the kidneys with silk, there was a statistically significant relationship between the fall in lymphocytes and the degree of hypertension (166). NaCl, ACE, and DCA caused pressor effects in hypertensive rats. The lymphopenia produced by

caloric restriction and a pyridoxine-deficient diet had no influence on the blood pressure.

It was found that there was a production of hypertensinogen in the presence of 11-oxycorticosteroids. No such increases were noted with DCA dosages which caused hypertension. The increase in hypertensinogen produced by ACTH and corticosterone administration is slow in developing and lasts a few days after cessation of medication. Although DCA elevated the blood pressure, no increase in hypertensinogen was noted (167).

By dividing the total urine corticosteroid into freely water-soluble and poorly water-soluble fractions, differences were observed in the percentage of these fractions found in urines of normal and toxemic pregnancies. There was a larger output of total corticosteroids in toxemic pregnancy, reflected chiefly in an increased percentage of the poorly water-soluble substances. Since, if DOC were present, it would be in this poorly water-soluble fraction, the possibility is offered that DOC-like material may be of some importance in the pathogenesis of eclampsia. The poorly-soluble fraction was also greater in pregnant than in nonpregnant women (168). The administration of DCA with salt to rabbits produced experimentally a picture resembling that of "toxemia of pregnancy." Though it is suggested that no complete replica of human toxemia can be reproduced in subprimates, these results favor the view that DCA-like substances are involved in human toxemia (169). The eosinopenic effect of ACTH was normal in the third trimester of normal pregnancy, but in toxemic pregnancies there was observed a stronger response, leading the authors to suggest an increased sensitivity of the adrenal cortex to ACTH in toxemias of later pregnancy (170).

A review of the use of adrenalectomy in cancer (171) and the physiological study of adrenalectomized patients when taken off adrenal steroids have added to the understanding of adrenal function in the human. It is quite apparent that the adrenal cortex produces estrogens (172). Also adrenalectomized patients cannot be without hormone for more than two days, as they become lethargic and nausea appears. Oddly enough, there is reported an antidiuretic effect when the patients receive no cortisone, and diuresis results when they are placed back on hormone therapy. These results indicate a state of water intoxication in the adrenalectomized patient kept without adequate hormone therapy (173).

#### THE PITUITARY-ADRENAL SYSTEM AND STRESS

Considerations of the role of the pituitary-adrenal system in stress responses involve: (a) the problem of the activation of the system by some mode of neurohumoral stimulation; (b) the nature of the secretory response of both the pituitary and the adrenal cortex; and (c) the question of specific secretory responses by the cortex and the nature of the somatic effectors governed by the adrenocortical secretion.

Injectons of epinephrine, or stresses which induce endogenous epinephrine

secretion (insulin and hypoxia), result in increased electrical activity of the posterior hypothalamic nuclei and the mammillary body. Other regions of the hypothalamus and the cerebral cortex were not similarly activated (174). These states of activity have been correlated with eosinopenia, and cauterization of these areas renders ineffective or greatly reduces the eosinopenia of stress (175). The areas involved are basically the same as those described by Hume (176) and also by Harris (177). A more direct index of adrenal activity such as the measurement of blood steroid is indicated since these studies were conducted using eosinophiles (175, 176) and lymphocytes (177) as indices, and these indices are not beyond criticism as measures of adrenal function.

The mediator of the hypothalamic region to the pituitary is still a matter of conjecture. At present it is assumed that the effect is either through a neurohormone which passes to the pituitary by the portal circulation (178) or directly neural (179). Attempts have been made to produce an extract of the hypothalamus (176, 180). There is some indication that one of these extracts has some effect on the blood elements (180).

Since there was a difference in the responses of eye-grafted pituitary preparations to stresses such as noise and immobilization as against cold stress and traumatic injury, it is proposed that various forms of stress use different mechanisms for pituitary discharge (181). Neurogenic stresses (noise and immobilization) presumably act directly through the central nervous system since transplanting pituitary to the eye nullified the pituitary discharge which normally occurs. Systemic stresses are those which cause pituitary discharge whether the pituitary is in its natural location or grafted in the eye.

The problem becomes more complicated with the findings of Harris *et al.* (178) indicating that a transplant of the pituitary in the temporal region of the brain, which receives adequate blood circulation, is not as stress responsive as that grafted in the hypothalamic region. The point of view is favored that the portal circulation is a necessary link to the hypothalamic-pituitary relationship, and that grafts of the pituitary do not necessarily assume normal secretory functions.

There are two major objections to accepting epinephrine as the stimulator of the adrenal-pituitary system in man: (a) the fact that epinephrine injection does not increase the blood 17-hydroxycorticoids (182, 184) or the urinary 17-ketosteroids (183) and corticoids; (b) the observation that the infusion of epinephrine into the human will cause initially some adrenal stimulation, but that this is followed by a period of adrenal-pituitary blockade (185). This blockade phenomenon is also observed in mice (186). Further evidence by direct measurement of epinephrine in the blood indicates that epinephrine is not responsible for the discharge of the adrenal-pituitary system (187).

Protection by blocking autonomic nervous system impulses indicates the



involvement of autonomic nervous function in the degree of stressability (188, 189). However, this is concerned with the survival of animals following stress rather than with the role of the autonomic nervous system in adrenal-pituitary discharge. Apparently overactivity of the sympathetic nervous system decreases survival in stressed animals. The involvement of the central nervous system in pituitary activation is further indicated by the results where electroshock causes an increase in adrenal weight which is nullified by anesthesia (190).

Eosinophiles continue to be a subject of much research, especially with regard to their use as an index of adrenal function. Eosinopenia appears to be due to the stimulation by adrenal hormones of macrophage ingestion of eosinophiles (191). Cold stress does not eliminate the diurnal fluctuation of eosinophiles in the mouse (192), and the past history of the animal is important since continued venesection for sampling purposes causes a steady decrease in the eosinophile count (193). On the other hand, continued handling has no effect on the counts in cows and sheep (194). It is assumed that cows and sheep have a sluggish pituitary-adrenal system. Strain and sex differences have been described in inbred mice with respect to response to adrenal cortical hormone (195). Degenerating eosinophiles have been described in the blood (196) and in lymphatic tissue (197).

Since eosinophiles have been shown to decrease where no increases in blood steroids were apparent and no increases in urinary output found, some doubt has been expressed concerning its use as an index of adrenal function. Further evidence of unsatisfactory results obtained with the use of eosinophiles as an index of adrenal function has been presented (198 to 201). It is now recommended that in testing adrenal function the blood 17-hydroxycorticosteroids should be estimated in addition to the eosinophiles (202, 203). It has been found in adrenalectomized dogs that doses of epinephrine which cause no eosinopenia, when given with cortisone (in noneosinopenic doses) evoke a marked eosinopenia. This action, indicating the synergistic effect of cortisone and epinephrine in the production of the eosinopenia, is another example of the permissive effect of adrenal hormone (204).

It is quite clear that the stress of irradiation plus doses of cortisone are synergistic in the production of lethal infection (205, 206), reduced resistance to cold, and other environmental stresses (207). The one report which deviates somewhat from these findings indicates that head irradiation alone, in similar doses leads to some protection against stress (208).

When oxygen in high concentration (90 to 98 per cent) is given to hypophysectomized animals there is a less toxic effect than in the normal animal (209, 210, 211). The main feature is pulmonary damage which presumably occurs due to the absorption of  $\text{CO}_2$ . Adrenal cortical secretion augments the death or injury rate but is not essential. This is claimed to be the first case where adrenal steroids exacerbate rather than alleviate results of stress.

In studies of phagocytosis in relation to pituitary-adrenal activity and



stress, there was found increased activity at the initiation of the stress, reduction to normal on adaptation to the stress, and a return to increased activity at the exhaustion stage. ACE and ACTH normalize these effects (212). "Stress lymphocytes" as differentiated from the effect of adrenal hormones on lymphocytes have been described (213). Further studies have been made on the action of steroids on lymphocytes and lymphatic tissues (214, 215).

Since depletion of ascorbic acid following unilateral adrenalectomy can be inhibited by the prior injection of cortisone, and ACTH then given depletes the vitamin C content of the adrenal, it is suggested that this be used as a basis for the bioassay of ACTH (216). DCA has been used as a pituitary blocking agent in a similar condition with satisfactory results (217). Cortisone by continuous intravenous injection failed to protect normal rats given histamine (218).

No effect on the adrenals of hypophysectomized rats subjected to the stress of scalding under acute conditions was found. However, under chronic situations with the same stress there was removal of adrenal lipids and an increase in the volume of cell nuclei of adrenal tissue (219). These results point to autoactivity of the adrenal cortex.

Estradiol monobenzoate causes increased release of ACTH into the plasma as well as accelerated formation of ACTH in the pituitary (220). With the standardization of experimental traumatic shock (221), studies indicate the possibility of bioassay by this procedure (222). Apparently Compound F is twice as effective as cortisone in this assay (222). It has also been shown that with continuous intravenous administration of ACTH the work output of adrenalectomized-hypophysectomized rats is increased with as little as 0.10 of an I.U. of ACTH per rat per day. Two units restored work output to normal levels, while 5 to 10 units led to supranormal outputs. Four to six mg. per day per rat of cortisone increased the work output to 22.4 per cent above normal (223, 224, 225). In the study of the effect of cortisone on striated muscle contraction, there was found an immediate increase of amplitude and maintenance of responses to indirect electrical stimulation after intravenous or intra-arterial injection of cortisone hemisuccinate. Cortisone increased the resistance of muscle to ischemia resulting from arterial occlusion (226).

The wild rat endures stresses, e.g. cold, loud noise and induced fighting, without decrease in adrenal ascorbic acid content or stainable lipids. The domesticated species show the usual responses to stress. ACTH does stimulate the adrenal of the wild rat, but large doses are necessary as compared with those which will stimulate the adrenal of the domesticated animal (227).

After salicylic acid administration, a decrease in ascorbic acid content of the adrenal is observed (228) with increased ACTH measurable in the blood (229). Of a group of salicylic acid derivatives tested *p*-aminosalicylic acid and *p*-hydroxysalicylic acid were the only compounds which would not reduce ascorbic acid content (228). Hypophysectomy abolished this effect

(228). Glycine potentiates the salicylic acid effect (230). On the basis of some clinical observations and parallelisms observed in serum cholesterol after ACTH and salicylic acid were given to rheumatic fever patients, the point of view that salicylic acid acts through the pituitary-adrenal system is favored (231).

These results must be viewed more critically in view of the finding that salicylic acid does stimulate the adrenal pituitary system, but that it will act therapeutically in the absence of the adrenal or the pituitary (232). Interestingly, although salicylic acid inhibits fibrinolysin protease and the *in vivo* effect is related to the antifibrinolysin effect *in vitro*, the two most used compounds, acetylsalicylic acid (Aspirin) and acetophenetidine, are without effect on fibrinolysin (232). Acetylsalicylic acid apparently has no effect on the eosinophiles or urinary steroid output (233). Most striking is the depression of glycosuria in the diabetic rat by acetylsalicylic acid which mitigates against its action as a pituitary stimulant (122, 123).

In spite of a three- to five-fold increase in adrenal cholesterol after the feeding of rape seed oil [the active factor has been found to be erucic acid (235)], there is no alteration in the capacity of the adrenal to respond to fasting, water load, or insulin administration (234).

Several organic compounds have been reported to interfere with the steroid metabolism of the adrenal cortex. Anethole (236) and DDD (237) inhibit activity of the zona reticularis and fasciculata but are without effect on the zona glomerulosa. Amphenone B (238, 239, 240) causes increased reactivity of the adrenal cortex with a blocking effect on the thyroid (238).

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# THE PARATHYROIDS<sup>1</sup>

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In 1948 extensive reviews of the physiology of the parathyroid gland were published by Greep (1) and by Albright & Reifstein (2). In this review an attempt has been made to summarize the more important contributions to this field that have appeared in subsequent years. In the limited space available, it has not been possible even to list all the articles that have dealt, directly or indirectly, with parathyroid physiology; this is especially so with regard to clinical material. It is hoped, however, that those articles that suggest an extension or modification of current theories have been included.

## PARATHYROID HORMONE

Attempts to isolate homogeneous active components from crude parathyroid extract have not been successful (3, 4). This difficulty has been a major obstacle to clarification of the mode of action of the hormone or hormones. With the use of Dowex and Amberlite columns and with counter-current distribution, Handler (3) separated several protein components from crude extract, but bioassay showed that the content, per milligram of nitrogen, of the factor which will raise the serum calcium in normal dogs was the same in all components. By dialysis, Handler & Cohn (4) did remove the capacity of crude extract to raise blood pressure without diminishing its content of calcium-raising factor or of the factor or factors responsible for increasing glomerular filtration rate and renal plasma flow.

## THE PHYSIOLOGIC ACTIONS OF PARATHYROID HORMONE

There is general, albeit not unanimous, agreement among investigators that the parathyroids exert an effect on the kidneys and an independent effect on bone. There remains, however, considerable controversy over which effect is "primary." A brief review of the arguments upon which the controversy is based may help to clarify the subsequent discussion.

The evidence in favor of a "primary" action of the parathyroids on the kidney is reviewed in (1) and (2). Albright & Ellsworth (5) observed that when parathyroid extract was administered intravenously to patients with hypoparathyroidism a rise in urine inorganic phosphate (urine P) preceded the fall of serum inorganic phosphate (serum P); when the hormone was stopped, the fall of urine P<sup>2</sup> preceded the rise of serum P. Furthermore, the

<sup>1</sup> The survey of literature pertaining to this review was completed in March, 1953.

<sup>2</sup> The following abbreviations have been used in this chapter: P (Inorganic phosphate); Tm (tubular maximum); GFR (glomerular filtration rate); ACTH (adrenocorticotropin).

product of serum calcium (serum Ca) by serum P remained roughly constant in such patients over wide variations in serum P. These observations could be fitted to a simple hypothesis if (a) the parathyroids, through the kidney, regulate serum P, and (b) bone destruction occurs when the serum solubility product of  $\text{Ca} \times \text{P}$  falls below a given value. Bone matrix calcification, on the other hand, could occur through local enzymatic elevation of P while the serum  $\text{Ca} \times \text{P}$  product favored reabsorption.<sup>3</sup> This hypothesis found support in the observations that hyperparathyroidism could exist without bone disease if Ca intake were adequate, that in hyperparathyroidism the feeding of large amounts of P could elevate the serum P and lower the serum Ca, and that parathyroidectomy is followed by a fall of urine P and a rise of serum P.

In this view, the osteitis fibrosa cystica seen with renal failure which has produced elevation of serum P results, not from the accompanying parathyroid hyperplasia, but from the metabolic abnormalities (acidosis, abnormal fecal P excretion, etc.) attendant upon the renal failure per se.

The evidence in favor of a "primary" action of the parathyroids on bone is reviewed in (1) and (2). Collip (10) noted that when parathyroid extract was administered to dogs the initial fall of serum P was followed by a rise, while the serum Ca was still rising. (The rising P was often shown to be accompanied by signs of renal failure). This was thought to contradict the "solubility product" principle (as regards bone dissolution), to be inconsistent with a primary renal site of action, and probably to indicate bone destruction as the primary site (11). This hypothesis found support in observations that parathyroid hormone could produce Ca loss without P loss, and that the serum P commonly falls upon removal of a parathyroid tumor which has produced bone disease.

*The effect of parathyroid hormone on bone.*—Although a number of experiments failed to demonstrate the efficacy of parathyroid extract in the absence of the kidneys (12 to 15), others gave contrary results. Using bone histology as a criterion, Ingalls and associates (16) and Selye (17) showed that the bones of nephrectomized animals showed definite changes upon administration of parathyroid extract. McLean, Bloom & Heller (18, 19) showed that parathyroid extract could affect bone histology in as little as 4 hr. after its administration. However, mediation of the kidneys was not excluded in these experiments. A similar qualification applies to the work of Engel (20), who showed that parathyroid extract produces rapid depolymerization of bone mucopolysaccharide with rises in serum glycoprotein levels and suggested this as the primary action of the hormone. Convincing evidence for a direct action of the parathyroids on bone was produced by Barnicot (21).

<sup>3</sup> In effect this requires different "solubility products" for matrix calcification and bone dissolution. For this reason, the hypothesis does not require that osteomalacia result from a lowering of the serum P as recently contended (6, 7). Extensive studies of the concentrations of Ca and P required in the media to allow calcification *in vitro* of rachitic cartilage have strongly supported, by analogy, the belief that the calcification of bone matrix is dependent on a minimal value of their product (8, 9).

who showed that pieces of parietal bone transplanted to the cranial cavity of mice, together with parathyroid tissue, underwent reabsorption on the side towards the parathyroid and deposition of new bone on the opposite side. Tissues other than parathyroid had little or no effect. This work was confirmed by Chang (22) who placed autogenous and homogenous grafts of parathyroid and other tissues against the parietal bones, left *in situ*, of mice and rats, with comparable results. Carnes (22a) found that parathyroid extract administered intraperitoneally produced histologic evidence of resorption of uncalcified matrix in the bones of rachitic rats and concluded that such an effect, which could not be secondary to changes in concentration of circulating Ca and P ions, indicated a direct effect of the extract on bone.

Indirect evidence for the action of the parathyroids on bone has been provided by studies of the serum Ca in nephrectomized animals. Talmage and co-workers (23) showed that the parathyroids are necessary for maintaining the serum Ca in nephrectomized rats and that parathyroid extract can return the serum Ca to control levels in rats nephrectomized and parathyroidectomized. Their animals were fasted overnight. This work confirmed that of Stoerk (24) in rats, and that of Ellsworth & Fitcher (25) and Monahan & Freeman (26) in dogs.

Stewart & Bowen (27) produced elevations of serum Ca above the normal in nephrectomized dogs, and showed that the depressed serum Ca in nephrectomized-parathyroidectomized dogs could be restored, with parathyroid extract. With the use of an "oxalate tolerance test" they showed that the serum Ca, acutely depressed by intravenous sodium oxalate in nephrectomized dogs, failed to return to normal levels in the absence of the parathyroids unless parathyroid extract was administered. In a later study (28) they used intravenously administered sodium citrate, showing that parathyroidectomized-nephrectomized dogs failed to respond with a rise in (total) serum Ca as did those subjected to nephrectomy alone. All of their animals were fasted overnight.

These studies provide evidence for an action of the parathyroids either on bone or on Ca absorption from the gastrointestinal tract. Since available evidence does not support the latter (29, 30), they afford presumptive evidence for a direct action on bone. Since the serum P in these experiments rose or did not change while the serum Ca was rising, they also cast doubt on the hypothesis that bone dissolution is dependent upon undersaturation with respect to a "solubility product." The latter hypothesis has recently been questioned on physicochemical grounds. Hodge (31) has emphasized the extreme variability in the values for such a product obtained by direct measurement. A number of workers (32) have emphasized the dissimilarity between bone salt and a simple "precipitate" of calcium phosphate. Clarification of the point awaits the development of suitable methods for determining calcium and phosphate ion activities in the fluids in question. In the studies in nephrectomized animals cited above, total Ca and inorganic P were determined in serum. The work of Freeman & Chang (33) suggests that infer-

ences concerning Ca ion activity drawn from total Ca are especially unreliable in the nephrectomized animal. These workers showed that circulating citric acid (and thus, presumably, diffusible nonionized calcium) undergoes a transient rise following nephrectomy, the rise roughly paralleling that of the total serum Ca. They showed, furthermore, (33) that the postnephrectomy rises in both Ca and citrate were generally, albeit not inevitably, eliminated by parathyroidectomy, thereby providing additional evidence for a nonrenal action of the parathyroids.

Dent (6) has recently questioned the "solubility product" principle in studies on man. He was able to lower the serum P with oral aluminum hydroxide and observed no corresponding rise in serum Ca. Hopkins and co-workers (34) raised similar objections on the basis of their *in vitro* studies of ultrafiltration of serum, in which they found that the Ca could be doubled or the P increased six- to eightfold before nonultrafiltrable Ca and P appeared. As they point out, such a system is not strictly comparable with the situation *in vivo* in which bone surface must obviously play a part. Munson and associates (116) found that after parathyroidectomy in rats fed a low calcium diet the fall of serum Ca preceded the rise of serum P, a result which they believe indicates an effect of parathyroid hormone on Ca independent of its effect on P. The possibility remains that small increments of serum P may have been nullified by deposition of Ca and P in bone matrix in rats so prepared.

*The effect of parathyroid hormone on the kidneys.*—Attempts to demonstrate a direct action of the parathyroids on the renal excretion of P have been numerous, with apparently conflicting results. Some of the conflict is attributable to differences in experimental methods. A brief consideration of renal P clearance (35) in general will help to clarify the present discussion.

Numerous *in vitro* studies (34, 36, 37) have shown that all of the serum P is ultrafiltrable save when the serum Ca or P are markedly elevated. *In vivo* studies with radioactive P were thought (38) to contradict this evidence, in that the specific activity of the urine exceeded that of the plasma for periods up to an hour after injection. This has been shown, however, to apply to virtually any filtrable substance (39) and to be a result of displacement of active material from the "renal dead space" (36, 40, 41). [For this reason it is impossible accurately to ascertain tubular reabsorption of a substance while its plasma level is changing, a rising curve giving clearance values falsely low, and a falling curve clearance values falsely high, with reciprocal errors in the estimated reabsorption. This limitation applies to several studies of the effect of parathyroid extract on renal P clearance (42, 43)]. There is no convincing evidence that P is "secreted" into the renal tubules (37, 44), although the possibility cannot be excluded (45).

Pitts & Alexander (46) and Schiess and associates (47) showed that increases in filtered P result in curvilinear increases in P reabsorption and excretion until reabsorbed P is maximal ( $T_{mP}$ ), when any additional P in

the filtrate is rejected by the tubules. The slope of the curves is such that, in the physiological range, the higher the initial serum P (and therefore filtered P) the greater the increment in excreted P from a given increase in "load." The  $Tm_P$  is roughly reproducible in the same subject. It may be lowered, however, by cortisone (48) and by general anesthesia (49) and may undergo a spontaneous fall during prolonged P infusion (37, 49). Whether the latter phenomena result from adrenal cortical stimulation has not been established. With well-trained animals undergoing infusion without struggling the spontaneous fall in  $Tm_P$  with time does not occur (49). Incorporation of potassium into infusion fluids has been found to raise  $Tm_P$  after it had fallen spontaneously (37). With high serum concentrations, some P becomes nonultrafiltrable (34). This presumably produces a "false" increase in calculated  $Tm_P$  if total serum P is used. "Osmotic" diuresis does not increase P excretion (50, 51).

Most investigators have found that parathyroid extract increases urinary P excretion. Some, however, have denied such an effect in normal subjects. Jahan & Pitts (52) found no P diuresis in normal dogs, but their studies were done 12 to 16 hr. after the hormone was administered. Furthermore, their data were largely collected during phosphate infusions when "maximal" phosphate reabsorption was occurring. Under such conditions the "load" of P is large and small changes in calculated reabsorption of P may be obscured in minor fluctuations of glomerular filtration rate. Milne (53) found no effect of parathyroid extract given intramuscularly in increasing urine P in normal man, although he did note such an effect in subjects with hypoparathyroidism. He does not state the times of injection or of urine collection, but the serum P is lower in all his normal subjects following injection, suggesting a previous increase in urine P. In another experiment, he showed more rapid excretion of phosphorus than of calcium when both calcium and phosphorus were injected simultaneously, a finding suggesting that even if parathyroid hormone affected bone primarily, phosphorus diuresis might be the first sequela. This would not, of course, explain lowering of serum P with the hormone. Fay and associates (42) found no effect of parathyroid extract given subcutaneously 3 to 24 hr. before measurements in normal or parathyroidectomized dogs. Their studies were done, however, with rising or falling serum P, and at high levels of serum P, subject to the limitations noted above.

Dent (6), in a preliminary report, states that he found "hardly any" P diuresis, but a slight rise in serum Ca in normal human subjects with parathyroid extract given intravenously; he noted that the preparation caused only moderate P diuresis in subjects with hypoparathyroidism. Stoerk & Silber (54) found an effect of parathyroid extract on urine P in parathyroidectomized rats, but none in intact animals.

A number of other investigators have shown P diuresis with parathyroid extract, but have not obtained data by which the renal mechanism could be



fully elucidated (see below) (5, 28, 55 to 59). The same qualification must be applied to the work of Brull & Carbonesco (60), who observed that transplanted kidneys of dogs parathyroidectomized 48 hr. earlier excreted less P than those of normal dogs. Stewart & Bowen (28) noted increases of urinary P excretion with parathyroid extract treated with formaldehyde and devoid of serum Ca-raising properties. It is possible that such preparations produce P diuresis by (presumably nonspecific) increases in GFR<sup>2</sup> and thus in P "load" as discussed below.

Other workers have observed P diuresis with parathyroid hormone but found that it could be explained by increases of serum P (a phenomenon suggesting a nonrenal site of action) or by increases in GFR (a phenomenon suggesting a nonspecific effect of impure hormone) rather than a specific effect on P metabolism (3, 4). Increases of GFR may by increasing the "load," cause absolute increases in both the amount excreted and that reabsorbed. Since feeding (61) or infusion (43) of P may also increase the GFR, and since such measures produce parathyroid hyperplasia, it has been suggested that control of GFR is a physiologic mode of action of parathyroid hormone, a possibility that cannot be rigidly excluded until pure hormone is available (62).

Crawford and associates (61), using endogenous creatinine clearance as a measure of GFR, found, in normal subjects given parathyroid extract intravenously, that increases of P excretion resulted from increases in both the GFR and the serum P. They suggest that parathyroid function be assessed by measuring the per cent of filtered P reabsorbed (P reabsorbed by tubules/P in glomerular filtrate). While this ratio would fall with increased P loss by any mechanism (increased "load," decreased reabsorption), it would not distinguish between mechanisms. The studies cited above (46, 47) show that any increase in P "load" results in an immediate fall in this ratio. Michie & Shorey found that P diuresis with parathyroid extract given intravenously to hypoparathyroid patients could be explained solely by increases in GFR. Hogben & Bollman (37) found that parathyroid extract increased P excretion as a result of increases in GFR and serum P in normal dogs and in parathyroidectomized dogs pretreated with parathyroid extract. One parathyroidectomized dog, not so pretreated, responded with a fall of P reabsorption. The latter results suggest the development of "resistance" to the hormone, noted by Collip, possibly an immune reaction to a foreign protein. They found no effect of parathyroid extract on  $Tm_P$  in either normal or parathyroidectomized dogs, although the latter had higher initial  $Tm_P$  values. Handler and associates (62) found that when parathyroid extract was administered intravenously to normal dogs, P excretion was increased because of rises in serum P and GFR, with increase in absolute P reabsorption (P reabsorption per cc. of filtrate did not increase). When they gave the extract subcutaneously, however, P diuresis resulted only from decrease of tubular reabsorption. In a later study (4) they observed elevations of serum

P (and therefore P excretion) when inactivated extract was given intravenously. This led to a repetition of the earlier studies in animals subjected to minimal manipulation. These animals showed no rise in serum P following intravenously administered extract, although the rise in GFR again occurred.

A number of investigators have found that parathyroid extract causes P diuresis largely through decrease in P reabsorption, most of them noting, however, that small increases in GFR did occur. Such were the findings of Klein & Gow (43) and McRory and co-workers (63) in essentially normal children; of Harrison & Harrison (64) in normal dogs; of Bartter (65) in parathyroidectomized dogs; of Kleeman & Cooke (45), Cargill & Witham (66), and Jacobs & Verbanck (67) in normal adults. The latter workers, in carefully controlled experiments with P infusion at moderate "loads," showed for the first time that parathyroid extract decreased P reabsorption under "Tm" conditions. Sirota (67a) found that the  $T_{mp}$  was low preoperatively in two patients with parathyroid adenomas, and that it increased four-fold in the postoperative period.

Cargill & Witham (66) further reported that glucose infusion raised phosphate reabsorption in normal human subjects and that parathyroid extract given together with glucose raised it still further. The former phenomenon has been denied by Levitan (68), who found that glucose infusion resulted in decreases in P reabsorption.

Kochakian & Terepka (55) and Bonelli & Sala (69) reported that toxic doses of parathyroid extract decrease kidney alkaline phosphatase in the rat, whereas "physiologic" doses do not.

*The effects of parathyroid hormone on tissues other than bones or kidneys.*—Imrie & Jenkinson (70) showed in 1933 that parathyroid extract restored towards normal the content and rate of formation of creatine phosphate in the muscles of parathyroidectomized cats, but did not exclude an indirect action (e.g., through serum Ca). Tweedy and co-workers (58) found that thyroparathyroidectomy decreased somewhat the rate of uptake of radioactive P by the muscles of rats. Tweedy & Campbell (57) found that the  $P^{32}$  uptake of the livers of normal rats given parathyroid extract was 20 per cent higher than that of controls. In the later work, however, the extract did not show consistent effects on the liver uptake in thyroparathyroidectomized rats, and was without any effect in nephrectomized animals.

Milne (53) suggests, from comparisons of the total amount of P lost in the urine immediately after administration of parathyroid extract and the amount disappearing from the extracellular fluid, that some must have entered tissue cells in response to the hormone. Martin & Perkins (71) in a preliminary report showed an increase in calcium-binding (per gm. N) by the serum albumin in patients with hyperparathyroidism. It will be of interest to learn whether this is correlated with the presence of bone disease, or with the elevation of serum mucopolysaccharide studied by Engel (20). Malmejac and associates (72, 73) reported that fibrinogen, alpha-globulin,

and prothrombin increased rapidly in the serum of dogs following parathyroidectomy. Daily injections of parathyroid extract, which required 15 days to reestablish normal serum Ca values, lowered fibrinogen values to normal in four days. Klotz & Elmaleh (74) found that sodium ferrocyanide could pass the "blood-brain barrier" in parathyroidectomized, but not in normal dogs. They noted that the calcium content of cerebrospinal fluid was lower in the former. Here, also, an indirect action is not excluded.

#### THE STIMULUS TO THE PARATHYROID GLANDS

In extensive chemical and anatomical studies in rabbits and rats, respectively, Törnblom (59) and Engfeldt (75) have reexamined the role of possible stimuli to parathyroid function, with especial reference to the question of a pituitary parathyrotropic hormone. Törnblom, measuring serum Ca, serum and urine P, and parathyroid weights, confirmed the findings of previous workers that diets high in P increase the weight of the parathyroid glands. In short-term experiments, he showed that P infusion in intact animals produced increases in urine P without significant rises in serum P, whereas in parathyroidectomized animals receiving parathyroid extract sufficient to keep the serum P normal in control experiments, it produced large increases in serum P without increases in urine P. Engfeldt, measuring the nuclear area, the ratio of cytoplasmic to nuclear area, and the total volume of the parathyroids, showed that a diet high in P produced significant elevations in the first and depressions in the second of these indices within five days, whereas significant elevations in the third were not observed until 10 days had elapsed. Crawford and associates (61) measuring parathyroid weights and serum and urine P in rats given diets of widely varying P content, found that increases in the P intake such as to produce large increases in the urine P produced only slight increases in the serum P but increased the weights of the parathyroids and produced therein histological evidence of activity.

Törnblom found the parathyroid glands of hypophysectomized animals to be smaller than those of control animals on similar diets, as did Engfeldt, who observed concomitant decreases in nuclear area and in the ratio of cytoplasmic to nuclear area.<sup>4</sup> Both workers found the serum P to be lower in the hypophysectomized animals and concluded that the effect of the pituitary is primarily on serum P, which in turn influences the parathyroids. They both supported this conclusion by showing (a) that hypophysectomy lowers the serum P of parathyroidectomized animals, and (b) that pituitary extract (Törnblom) and growth hormone (Engfeldt) will further raise the serum P in hypophysectomized-parathyroidectomized animals. Törnblom further found that ACTH<sup>2</sup>, adrenal cortical extract (Eschatin), and posterior pitui-

<sup>4</sup> This ratio falls, according to Engfeldt, with both increases and decreases of parathyroid activity. With the former, the fall results primarily from increase of nuclear area; with the latter, from decrease of cytoplasmic area.

tary extract raised the serum P in hypophysectomized-parathyroidectomized animals. Engfeldt, on the other hand, found that ACTH and adrenal cortical extract did not produce histological evidence of parathyroid overactivity in hypophysectomized rats (a finding based on few animals in which parathyroid volumes were not given) and that adrenalectomy produced elevations of serum P with concomitant histological evidence of parathyroid stimulation. The belief that there is no direct pituitary control of the parathyroids is supported by the work of Brolin (76) who found no significant increase in pituitary weights after parathyroidectomy in rats.

Törnblom suggests that growth hormone, ACTH, and pancreatic diabetes may all influence the serum P, and thus the parathyroids, through an influence on carbohydrate metabolism, providing a possible clue to the clinical association of pituitary, islet cell, adrenal, and parathyroid tumors (see below).

Both Törnblom, and Crawford and associates suggest, from simultaneous observations of serum Ca, serum P, and parathyroid weights, that elevation of serum P without depression of serum Ca may stimulate the parathyroids. Indirect support to the concept that the level of the serum Ca controls the secretion of parathyroid hormone was provided in the interesting calcium infusion studies of Howard and co-workers (77). They infused calcium gluconate-glucoheptonate into normal human subjects and noted an increase in serum P and a decrease in urine P, which they interpreted as evidence of decreased endogenous parathyroid hormone activity. At no time did any serum P become nonultrafiltrable following the infusion, as determined by the Laviets technique. This does not, of course, demonstrate with finality that it all remained permeable to the glomeruli. A lack of these responses in patients with hyperparathyroidism suggested the use of this as a diagnostic test. They further noted that the amount of P added to the extracellular fluid was in excess of the amount excreted in the control period and, indeed, that it accumulated during a four-hour period in which urine P was sometimes actually elevated, a finding suggesting that cellular P became extracellular during the infusions. Sen and associates (78) observed that glucose given intravenously to rabbits caused moderate reduction in serum P and marked elevation in serum Ca, and believed these changes to result from stimulation to the parathyroids. It was thought that insulin played no part. Malcolm and associates (79) observed marked parathyroid hyperplasia in rats treated for 56 to 122 weeks with thiourea and related compounds. It was not prevented by the simultaneous administration of thyroxine. In 9 out of 33 rats osteitis fibrosa cystica could also be demonstrated. The possibility that renal failure contributed to both phenomena cannot be excluded.

#### PARATHYROID HORMONE ASSAY

Several workers have attempted to find a method of parathyroid hormone assay less expensive and cumbersome than that of Collip. As indices

of parathyroid hormone activity, Opienska-Blauth (80) used the increase of urinary calcium excretion by mice, Tepperman and co-workers (81) used the fall in serum P in 3 hr. of fed rats treated subcutaneously, Biering (82) used the rise in serum Ca in 18 hours of fed rats treated subcutaneously, Munson and associates (117) used the prevention of the fall in serum Ca in 6 hr. post-parathyroidectomy of rats fed a diet low in calcium, and Rubin & Dorfman (83) used the excretion of  $P^{32}$  in 3 hr. of thyroparathyroidectomized rats treated subcutaneously. All workers obtained a "log-dose" response, the last group claiming by far the greatest sensitivity for the method. As discussed above, the rise in urinary excretion of P following administration of parathyroid extract may be in part a nonspecific phenomenon.

#### CLINICAL DISORDERS OF THE PARATHYROIDS

A host of case reports of hyperparathyroidism has appeared. Underdahl and associates (84) have presented eight cases with tumors of the parathyroids (multiple in all) associated with proven tumors of the islet cells or severe hypoglycemia, and, in four, pituitary adenomas. Two had adrenal cortical adenomas as well. They reviewed the literature, finding 14 similar cases. Black & Ackerman (85) have reviewed 23 cases with parathyroid tumors, two of which had multiple adenomata of other glands. Sommers & Young (86) have reported six cases of pale oxyphil cell adenomas producing hyperparathyroidism and have reviewed the literature, stressing the frequent clinical association of hyperparathyroidism and pituitary disease. Castleman (87) has reviewed the pathology of parathyroid tumors, as have Woolner and associates (88), the latter summarizing 140 cases of primary hyperparathyroidism from the Mayo Clinic. Castleman & Cope (89) have reviewed 11 cases of primary hypertrophy and hyperplasia of the parathyroids, stressing the predominance of renal stone and the paucity of bone changes in these patients. All cases had persistent hypophosphatemia after operation.

Albertini and associates (90) report the presence of a single capsulated functioning parathyroid adenoma in the liver, leading them to reexamine the criteria for a diagnosis of parathyroid carcinoma. Many observers have noted the coexistence of gastric and duodenal ulcers with hyperparathyroidism. Hyperplasia of all parathyroids, with osteitis fibrosa cystica, was reported (91) in a newborn child whose mother had had hypoparathyroidism for 20 yr.

The subject of idiopathic hypoparathyroidism has been reviewed (92). Hypoparathyroidism has been reported in three brothers (93) and in two sisters (94). Temporary hypoparathyroidism was produced in a 14-year old boy given 4 millicuries of  $I^{131}$  for hyperthyroidism (95). Spira (96) has made the intriguing suggestion that hypoparathyroidism may result from fluoride poisoning. Attempts to graft beef (97) and human (98) parathyroid tissue into patients with hypoparathyroidism have been carried out, the latter with some apparent success.

Pseudohypoparathyroidism has been the subject of considerable interest and controversy. Essentially, the diagnosis rests on two features: the persistence (and, indeed, hyperplasia) of parathyroid tissue, and resistance to exogenous parathyroid hormone, in patients showing the chemical changes of hypoparathyroidism (2). Since parathyroid biopsy has generally not been obtainable, the reported cases have been diagnosed on the basis of the Ellsworth-Howard test (56) together with the commonly associated metacarpal and metatarsal changes, the short stature, and the "round face." Unfortunately, the Ellsworth-Howard test may give false negative results if the hormone is inactive (99) or if the patient is "immune" to it, and probably false positive results if the hormone has a marked effect on the GFR. These considerations may explain the anomalous results of Schüpfbach & Courvoisier (100), who found P diuresis with parathyroid extract in a case showing the anatomical features of pseudohypoparathyroidism, and of Martin and co-workers (101) who failed to obtain P diuresis with the extract in some normal subjects and in two patients with hypocalcemia and hyperphosphatemia, one with and one without the anatomical abnormalities of pseudohypoparathyroidism. A patient with pseudohypoparathyroidism and unexplained osteoporosis was reported by Reynolds and associates (102).

Familial pseudohypoparathyroidism has been reported twice (103, 104). Albright and associates (99) have suggested the diagnosis "pseudopseudohypoparathyroidism" in a patient with all the anatomical features characteristic of pseudohypoparathyroidism but with normal blood chemical values. They suggest that a genetic disorder, which may or may not be "complete," is responsible for the latter syndrome.

Nervous system changes in parathyroid disease have been reviewed (105). Probenecid (Benemid) has been reported to lower the serum P and raise the serum Ca in hypoparathyroidism (106) and to have no effect on renal reabsorption of P (107).

#### OTHER STUDIES

The innervation of the parathyroids has been reexamined by Raybuck (108), who finds secretory fibers ending on or in the secretory cells. Schneider (109) showed a close anatomical relationship between the parathyroids and the carotid body in birds. Rucart (109a) has studied the morphology of parathyroid cells in a wide variety of mammals. He believes that all cell types found originate as basic (chief) cells, which may develop along a "clear series" with progressively greater degrees of vacuolization, or a "dark series" with progressively greater numbers of oxyphil granules. He concludes on morphologic grounds that there are two types of hormone produced. Czerski (109b) has reviewed the subject of parathyroid histology, with especial reference to attempted correlations of function with morphology. The two studies serve to emphasize the need for co-operative studies between physiologists and morphologists in this field.

Dolgina & Kaplan (110) produced hypercalcemia and moderate hypo-

phosphatemia in normal rabbits, rats, and dogs by placing sterile suture material in the parathyroid glands. They could hasten the return of serum Ca to normal in rabbits with three parathyroids removed by placing a suture in the fourth.

Parathyroid extract has been shown to allow more normal dentition in *ia* rats, in which osteopetrosis would normally prevent the teeth from emerging (111). Hereditary osteopetrosis has been reported in rabbits which show low serum Ca, high serum P, and hyperplastic parathyroid glands, a condition reminiscent of pseudohypoparathyroidism (112). It will be recalled that Selye produced a similar bone condition in rats by chronic administration of small doses of parathyroid extract (113). Parathyroid extract was found to allow partial regeneration of excised paws of 4- to 15-day-old rats, presumably by hastening resorption of bone in the stump (114). Parathyroid extract, given with or without dimercaptopropanol (BAL), had no significant effect on the excretion of lead, largely deposited in the bones, of rabbits injected with lead acetate 14 to 21 days previously (115).



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## REPRODUCTION<sup>1,2</sup>

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The furthering of our fundamental understanding of physiological reproductive processes is required if productivity control is to be obtained. To aid in the attainment of this goal, a survey of the past year's contributions, with limitations, is here presented.

### HYPOPHYSIS AND GONADOTROPHINS

Further histochemical and cytological studies on the hypophysis in man (1, 2, 3) and other mammals (4 to 8) have been published, but the number of cell types (9) and cell source of gonadotrophins remains controversial for LH<sup>2</sup> may not evolve from acidophiles (10, 11). However, pituitary basophile population does correlate with gonadotrophin content in six strains of mice (12), and additional evidence favors fetal pituitary function (13, 14, 15). Gonadotrophic activity could not be detected in glands from the newborn, but a positive response is obtained with material from a four-year-old child (16). In adult man, gonadotrophins in the hypophysis and urine of both sexes were appraised for FSH<sup>2</sup> and LH content in hypophysectomized rats. The homogenate of reasonably fresh material was active at 3 mg. levels in both sexes of test animals and equal FSH and LH activity was assigned to the human hypophysis of both sexes. Urinary gonadotrophins, however, favor FSH to LH by 2 to 1 with slightly more LH in the female than the male (17, 18, 19). Human urinary gonadotrophins were used clinically without antihormone formation (20), a usual source of difficulty (21) which may be influenced by cortisone (22). Gonadotrophins in ultracentrifuged rat pituitary are associated with the small granule fraction (23).

A constant and maximum amount of gonadotrophin is present in ewe pituitaries during anestrus followed by a decrease at ovulation and a return to anestrus level in 16 to 17 days (24). During pregnancy, rat pituitary gonadotrophins exhibit a cyclic pattern with more peaks and greater hormone content in the last week (25). Pituitary gonadotrophin content in the castrated monkey is reduced by 100  $\mu$ g. but not by 10  $\mu$ g. of estradiol. The lower dosage of estrogen combined with 2 mg. of progesterone, however, is effective, and the depleted gland requires 20 days for recovery (26). In women, single

<sup>1</sup> The literature survey pertaining to this review was concluded in late June, 1953.

<sup>2</sup> The following abbreviations are used in this chapter: FSH (follicle stimulating hormone); LH (luteinizing hormone); ACTH (Adrenocorticotrophin); DCA (desoxycorticosterone acetate); DNA (desoxyribonucleic acid); RNA (ribonucleic acid).

<sup>3</sup> Grateful acknowledgment is made to Mrs. Shirley McCormack for assistance with the bibliography.

injections of estrogen given prior to ovulation cause release of gonadotrophins (27).

The assay of gonadotrophins can be markedly improved with inbred rats (28), with the amount of ovarian tissue available to respond as a variable between strains (29). Ovarian weight response, however, may not be a justifiable end point for, should ovulation be desired, then comparative extract activities may assume a new dosage relationship (30). Parabiotic mice may not provide continuous hypophyseal stimulation to the normal partner as estrogen eventually controls the castrate hypophysis. This can be overcome with parabiotic triplets (31). Responses to administered gonadotrophins are varied (32). To mention a few, one finds correction of sterility in hypogenital rabbits (33) and the activation of ovocyte and follicular development in prepuberal monkeys (34).

#### REPRODUCTION IN THE MALE

*Testis.*—Human testis biopsies from newborns and up to 16 years of age reveal age 10 as a critical time in development. Prior to this age, tubules exhibit little tortuosity and are lined by single layers of spermatogonia-like cells. Activity increases sharply after 10 years of age, tubular diameter doubles, spermatocytes appear, Sertoli cells evolve from undifferentiated cells and Leydig cells seen only in a testis from a newborn appear again and acquire lipid (35, 36). Illness at this time may cause sterility as the tubules are never normal if Leydig cells are abnormal or absent, and a cryptorchid testis soon becomes sclerotic. Histochemically, the human testis interstitial tissue contains lipid, cholesterol, alkaline phosphatase, and lipase, but no glycogen. Mature and immature Leydig cells differ. Glycogen, lipid, and phosphatase appear in spermatogonia, growing primary spermatocytes, and Sertoli cells. Tubular glycogen decreases in sterility; Sertoli cells acquire ascorbic acid and more lipid with aging (37 to 40). The testis of man, unlike that of the rat, lacks periodicity in spermatogonial divisions (41). The rat testis has been analyzed for RNA (ribonucleic acid) and DNA (desoxyribonucleic acid), as well as for acid soluble and lipid soluble phosphorus, from immaturity to maturity. The absolute amount of each fraction increases with testis growth, but the relative concentrations decrease (lipid phosphorus excepted). Apparently the loss in cytoplasm and reduction in chromosome number reduces the relative RNA<sup>2</sup> and DNA<sup>2</sup> (42). Chorionic gonadotrophin increases the uptake of P<sup>32</sup> in the rat testis with incorporation specifically in the coenzyme fraction. Thus, the hormone may act to incorporate inorganic phosphorus into the cyclophorase system or on phosphate transfer from pyridine nucleotide to acceptor systems (43).

Androgen production by the fetal testis has gained support (44), but test methods employing prostatic response to implants may be nonspecific, and chick comb is recommended (45). Androgen is elaborated by the Leydig cells, but the presence of estrogen in the testis and urine permits speculation on

what cells secrete this steroid. Further evidence supports the tumorous Sertoli cell as estrogen productive (46). However, chorionic gonadotrophin stimulates Leydig cells in man to increase estrogen excretion (47). What part the seminiferous tubule plays in controlling the hypophysis is still speculative. Minced monkey testis remained viable for eight weeks in human albumin, but secretions were not estimated (48).

Weekly injections of  $I^{131}$  do not alter mouse testes (49), but x-rays in fish (50) and dogs (51) destroy the tubules. A modest increase in rat testis nucleic acids follows x-rays (52). In certain doses, direct irradiation lacks effect, in contrast to whole body irradiation, the latter inhibiting spermatogonial mitoses for four weeks, the possible duration of the rat spermatogenic cycle (53). Unlike x-rays, which stop spermatogonial mitoses quickly (54), death permits activity in these cells for 16 hr. (55). Spermatogenic arrest and testis atrophy can be induced by nitrofurane compounds orally or by injecting a nitrogen mustard [tris (2-chloro-ethyl)amine] (56, 57). Enheptin (2-amino-5-nitrothiazole), used for treatment of blackhead in birds, has now been shown to induce testis atrophy in cockerels (58).

General studies indicate that the testis varies in rate of development in the ram (59), is adversely affected by high ambient temperatures (60) or by destruction of the vesiculoprosthetic ganglion (61), and is mildly influenced by hypoxia (62). In wild birds, gonadal lipid is inversely proportional to sexual display (63).

*Accessory structures.*—Ductuli efferentes and ductuli epididymides contain lipid, cholesterol, glycogen, phosphatases, basophilia, and secretion granules in the epithelium (37). The function, particularly of the efferentia, is in part, the removal of fluid and pigment coming from the seminiferous tubules (64). Interference with epididymal blood supply may cause testis atrophy (65).

Male accessory sex organs increase in total nitrogen and lipid as the rat matures, and these components, as well as others, are influenced by androgen (66, 67, 68). Studies on other major metabolisms indicate that androgen influences the conversion of acetic acid to long chain fatty acids in the prostate but has little influence on the respiration-coupled synthesis of phosphorylated compounds (69). Castration reduces aspartic and alanine transaminases in the accessory organs involving these enzymes in amino acid deamination (70). In the guinea pig, the aerobic and glycolytic pathways for glucose metabolism may operate simultaneously in the seminal vesicle (71). Beta glucuronidase, citric acid, carbonic anhydrase, and zinc in the accessory organs are subject to species variation (72 to 75). Seasonal variation in bird accessory organs is androgen-controlled, as no response is elicited with estrogen (76).

*Spermatozoa and semen.*—The sperm head consists of a lipoprotein and a basic protein together with a nucleic acid. The lipoprotein is 25 per cent phospholipid and cholesterol (77). Studies on sperm cytology, on amylase



content, and in counting live and dead bull sperm have appeared (78 to 82). An abnormal acrosome is associated with sterility (83), but the antigenicity of spermatozoa remains a question (84).

Human sperm plus glycerol may be stored in dry ice for three months with 67 per cent survival (85). Nevertheless, sperm must be treated with care as repeated washing will greatly reduce motility, although some protection is afforded by KCl. Resuspension of washed sperm in seminal plasma restores motility. Dilution of ram or bull sperm in glucose-saline decreases motility, but salt is not the effector, and plasma proteins offer partial protection (86). Sperm motility is favorably influenced by glycine (87) and by ergothioneine, as cupric ion inhibition is counteracted (88). Considerable interest has been placed in semen fructose and rate of fructolysis as a measure of fertility, although bull sperm utilize glucose in preference to fructose (89). Normal fructose levels maintained by androgen in castrated bulls do not mean normality, as fructolysis of normal sperm is subnormal in this semen, possibly because all amino acids are not held at normal levels (90). Normal human semen contains at least nine amino acids and also pepsinogen (91, 92). In bull semen, sodium sulfite is the major reducing substance (93). A yeast-stimulating agent containing sulfur is in semen and may account for the lower motility of epididymal sperm as this compound is in a bound, inactive form in the epididymus (94).

*Androgens.*—Interest in androgenic action of longer duration than obtained with testosterone propionate has incited a study of esters and vehicle (95, 96). Testosterone valerate and isobutyrate offer clinical promise based on ketosteroid excretion (97), and extended nitrogen retention is reported with the cyclopentylpropionate and phenylacetate (98). Androgens with a predominant anabolic action continue to be desirable, and some success has been attained (99, 100, 101). Another approach could involve hormone antagonisms, a subject replete with various studies and of unique value when the antagonist itself is inactive, as 11-hydroxyprogesterone (102).

Androgen, in an unconjugated form, is excreted in the feces (103) and is the major excretory pathway following testosterone-4- $C^{14}$  injection (104). Ligation of the bile duct directs the excretion to the urine and cannulation of the duct permits direct recovery. Adrenal androgen may be metabolized corticosteroids, for the latter contribute to ketosteroid excretion in rats (105).

No advantage was afforded by androgen treatment of premature infants (106), and this could be undesirable therapy in view of the delay in development of the reproductive system of mice following one pre-weaning injection of androgen (107).

*Male sex behavior.*—Ejaculation can be induced in mice with yohimbine and blocked by *N*-(2-chloroethyl)dibenzylamine (Dibenamine) (108). Major motor pathways for the ejaculatory reflex which respond to electrical stimuli are sympathetic, and effector organs are adrenergic (109, 110). In the guinea

pig, careful measurements of sex drive reveal that many individual differences exist. Castration lowered sex drive to a uniform low level, and restoration to precastration level was unrelated to androgen dosage (111).

#### REPRODUCTION IN THE FEMALE

*Estrous cycles.*—Complete quiescence of cyclic phenomena seems unlikely during anestrus in ewes (112), and mating continues during pregnancy in hamsters at times corresponding to recurrent estrus (113). Increasing daylight hours when associated with the breeding season increases the ewe's responsiveness (114), and the full moon is associated with the greatest number of conceptions in Malayan forest rats (115). In the junco and quail, the period of uninterrupted darkness is critical in the photoperiodic response (116, 117) and spontaneous regression and a concomitant refractory period follows prolonged light stimulation (118).

Although initial vaginal opening is accelerated by cold (119), the rat's cycles thereafter exhibit prolonged proestrus (120). In the guinea pig's first cycle, vaginal opening normally lasts 10 days and retreats to 3.2 days by the fifth cycle, estrogen and progesterone injections having no effect (121). Progesterone, however, appears to be the causative agent in bovine metestrus bleeding (122), a species in which cervical mucous varies with the cycle (123).

While ligation of the ovarian pedicle leads to diestrus (124), ligation of the ovarian artery and accompanying nerves has no effect (125). Tubal ligation, however, is followed by continuous estrus and the formation of an estrogen containing capsular fluid. Rupture of the bursa restores the rat's cycles (126).

*Menstrual cycle.*—The cyclic vaginal smear may indicate ovulation (127) and provide an estimate of androgen production if 50 mg. of testosterone propionate is considered the antagonist of 1 mg. of estradiol benzoate (128). Estrogenic potencies determined by human assays place ethynyl estradiol as most effective with stilbestrol intermediate (129). Estrogenic potencies based on estrogen withdrawal bleeding in monkeys following single injections favor estradiol dipropionate as most active and emphasize the importance of prior treatment on threshold level (130). Estrogen effectively aids the healing of vaginal wounds in menopausal women (131).

Water, protein, and lipid components of endometria vary with the cycle. Water is maximal at midproliferative stages, a time when the other components are lowest (132). Aerobic glycolysis is maximal in secretory endometria, anaerobic glycolysis is minimal (133). Furthermore, in the secretory endometrium one finds the release of phosphate and the amount of phosphatases, cytochrome oxidase, and succinic dehydrogenase attaining a maximum, but estrogen alone will increase oxygen uptake (134 to 137).

Amenorrhea responds to low dose pituitary and ovary irradiation (138) and dysmenorrhea to androgens (139). However, the time of the menarche

and menstrual flow do not respond to the Singapore climate (140). Menstrual disorders associated with myxedema are frequently anovulatory, and effective thyroid treatment may imply increased release of LH (141). Assessment of the menstrual cycle by hormone assay has been reviewed (142) and the optimum time for insemination for conception selected (143).

The correction of secondary amenorrhea with cortisone (144, 145) may be a response to pituitary stimulation as urinary FSH in man is increased (146) and the number of follicles increases in the cortisone-treated rat ovary (147). However, cortisone does not release pituitary gonadotrophins in the rabbit (148).

*Ovary.*—The rat ovary acquires a uniform cholesterol content about 12 days of age, and hormone responsiveness is correlated with cholesterol deposition (149). Many other histochemical measures are used to estimate ovarian function from which Deane (150) concludes that basophilia is associated with cell growth; that steroids are formed in the theca, atretic granulosa, interstitium, and corpora lutea; and that ascorbic acid and phosphatases are rich at sites of steroid formation. Atresia favors an increase in glycogen, esterase, lipid, and phosphatase in the granulosa. Species comparisons must be made, however, for the normal hamster ovarian granulosa phosphatase concentration simulates atresia in rats (151). Perhaps further insight into ovarian function will be gained from isotope studies now essentially presenting distribution patterns (152, 153).

The rat ovary exhibits a rhythmic fluctuation in number of medium and large follicles of one size, with atresia of medium-sized follicles occurring between estrus and ovulation but rarely involving large follicles (154). The number of atretic large follicles, however, may be influenced by strain (155). Nevertheless, the source of ova for the follicles must be prepuberal or before birth as compensatory hypertrophy occurs without an increase in oocyte number (156, 157).

Follicles quite frequently undergo abnormal growth and become cystic and, while the cause is not known, cyst formation may follow estrogen administration (158, 159). Thyroid function too, is involved, as estrogen administration to hypothyroid rats markedly enhances cyst formation (160). Furthermore, hypophyseal thyrotrophin, but not gonadotrophin, is elevated in sterility cases associated with ovarian cysts. Cystic fluid contains estrogen and progesterone but no androgen, with estrogen more markedly reduced in comparison with normal follicular fluid than progesterone (161, 162). Control of ovarian cyst formation induced by transplantation to the spleen can be prevented by an ovarian transplant to the kidney with the estrogen controlling the hypophysis (163).

Ovarian weight is maintained with estrogen in hypophysectomized rats, and estradiol increases the total number of follicles and delays regression in follicular size. This steroid may accelerate growth of small follicles without increasing atresia (164). Parkes & Smith (165) have successfully transplanted

ovaries stored at low temperature for some months. The need for slow cooling in proper medium and rapid transplantation on thawing are important for a high percentage of takes. These ovaries develop follicles and corpora lutea at first, but follicles disappear in a month.

*Ovulation.*—Ovulation without heat occurs frequently in cows, and up to 3 per cent of nonlaying hens ovulate (166, 167). Furthermore, multiple ovulations comprise 13 per cent of the total in cows, but only 2 per cent twinning is observed. The importance of the neural link between the pelvis and hypophysis for the events of ovulation is further emphasized by sectioning the pelvic nerve. Neither ovulation nor pseudopregnancy follows copulation or cervical stimulation in these rats. Substitution for the uninformed hypophysis is obtained with progesterone (168). The neural link is also important in birds to synchronize ovulation with the events of a laying cycle, as a thread in the magnum reduces egg laying and again progesterone (or LH) will normalize activity (169). The nervous pathways involved are autonomic, and the use of drugs affecting this system indicates that 20 to 35 min. is required for ovulating hormone release in rats as compared with 2 min. in rabbits (170), with further work designed to include the cat (171). Neostigmine (Prostigmine), a parasympathetic stimulator, induces precocious vaginal opening (172). In the hen, unlike the rat, pentobarbital did not prevent ovulation (173), but some barbiturates may induce ovulation prematurely and also augment progesterone-induced ovulations (174). Progesterone may act favorably with gonadotrophins to induce ovulation (175 to 178) and an estimation of its occurrence has been made possible in monkeys by variations in negative potential (179).

*Female reproductive tract.*—The intravaginal route for estrogen is much more sensitive than the subcutaneous route (180) and may be related to the rate of increase in vaginal mucosal water and cell permeability to phosphate (181). Uterine epithelium also responds readily to estrogen (182).

During the estrous cycle, uterine DNA is constant but cyclic changes in RNA and glycogen are maximal at estrus or proestrus (183, 184), a time when estrogen is high (185). Estrogen-induced uterine growth shows that competitive steroid interaction and species factors exist (186, 187), but with this stimulus an increase in water, amino acid incorporation, enzymes, phosphorus incorporation, total oxidative metabolism, and glycolytic activity follows (188 to 191). Cell membrane changes and enzyme alterations come to the fore in suggested modes of action. Serious estrogen antagonism is obtained with 17-hydroxycorticosterone in which "esteroprotein" may be the active circulating estrogen (188). Inactivation of estrogen by liver homogenate is obtained with microsomes (enzymes?) and supernate (riboflavin?) (192), whereas enhanced estrone activity occurs with estronase from rabbit red cells (193). Preparation of 17-methyl- $C^{14}$ -estradiol reveals 86 per cent excretion via the feces (194).

Progesterone enhances estrogen to increase phospholipids, nucleic acids,

and arginase (195, 196) but also antagonizes estrogen action on the uterus and oviduct (197 to 200). The Hooker-Forbes progesterone assay reveals this steroid in primate and rabbit postpartum blood (201, 202), although the technic is under scrutiny (203, 204, 205). Increased progesterational activity is offered by 19-norprogesterone (206).

Development of deciduomata in traumatized uteri is not prevented by preexisting decidua (207), but progesterone requirements in mice are influenced by strain (208). Furthermore, pseudopregnancy is not induced as readily by electrical stimulation in mice as in rats (209). Deciduomata formation is associated with a marked increase in blood histaminase, and this enzyme increases in the uterus under progesterone stimulation (210). Furthermore, a decidual reaction follows local application of histamine (211). On the other hand, the rat uterus, while containing histaminase, does not respond to steroids but does exhibit an enzyme increase in the presence of decidua (212), which, incidentally, can be prevented by histamine antagonists (213).

Changes in the endometrium frequently overshadow myometrial contributions. Hormonal influences on the muscle reveal that estrogen increases whereas progesterone decreases the duration of a single uterine contraction time (214), and isometric tension depends upon the actomyosin concentration as influenced by estrogen (215). Total activity index of the cow uterus varies little in the cycle, but frequency and amplitude of contraction reflect hormone influences (216). Oxytocin released at insemination may contribute to the tetanic uterine contractions at copulation, apparently designed to aid sperm transport (217, 218).

*Fertilization and fertility.*—The presence of spermatozoa in the female tract precedes ovulation, but a delay of 2 hr. transpires before rat sperm penetration (period of capacitation) takes place (219). Time is very important, despite survival of ewe ova for 15 hr. (220), as delaying insemination 9 to 12 hr. after ovulation in rats reduces fertilized ova to 71 per cent and increases abnormalities to 43 per cent. The aged egg pronucleus fails to respond and fragmentation follows (221), or abnormalities may ensue (222). Rat ova, however, must reach the first polar body stage for fertility on transplantation. The ova may be fertile for 20 hr. of the rat cycle, part of the time being intraovarian (223), a possible insemination site in birds (224). Prenatal mortality is about 40 per cent in mammals, as some ova do not cleave and others degenerate at a later stage (225). Highly fertile rabbits exhibit fewer egg losses than potentially sterile rabbits (226). Mall considered fetal death as environmental and discounted defective germ plasm. Certainly maternal environment can contribute, but in the opossum a percentage of eggs are either not fertile or abnormal despite a normal environment. Moribund mouse ova are identifiable by failure to implant and to reduce methylene blue (227). The hormonal environment loses some importance if growth of ectoplacental trophoblast in the hypophysectomized male mouse eye may be

taken as evidence (228). Transplantation of 8 to 12 cell bovine eggs was successful in three of five cases (229), but this transfer of ova presents problems related to media, temperature, and time (230, 231). Best results, as represented by living young at term, are obtained in mice when four unfertilized ova are transferred in semen diluter (232). Rabbit eggs in a sperm suspension cause agglutination, but these eggs do not act on bull or mouse sperm, inviting attention to the fertilizin-antifertilizin mechanism (233) and also to similar studies with invertebrate material. These interesting studies involving fertilizins, polyspermy, and improved fertilization with glycine, to mention a few, can not be reviewed (234, 235).

Fertility problems related to artificial insemination in farm animals have involved modification of semen diluters, the value of adding antibiotics, storage temperature, and methods of evaluating the potential fertility of samples. Pyruvate metabolism as measured by  $QO_2$  of bull sperm appears to correlate with fertility records (236). Thyroid function influences reproduction and fertility, but species and hormone dosage must be carefully considered (237). Thyroidectomized female guinea pigs experience a reduction in fertility and in young born alive; male fertility is subnormal too. Thyroxine is beneficial in normal guinea pigs, increasing the young born alive above normal control levels (238, 239). Sulfaguanidine, which has a goiterogenic effect, induced 95 per cent sterility in the fourth generation of rats, but thyroid was not corrective (240). Short periods of estrogen administration may improve conceptions (241), but prolonged treatment generally decreases fertility (242) without permanent sterilizing effects even on repeat treatment in adult female mice (243). However, fertility of male offspring is seriously reduced by x-raying pregnant mice (244), and the mating of irradiated male rabbits to normal does increases the frequency of resorptions (245). In the face of these adversities, the delivery of a second litter by a rat without re-breeding, is recorded (246).

Phosphorylated hesperidin, as an antifertility factor, proved highly effective in 300 couples tested for 3 to 30 months without aftereffect (247). However, rabbit and rat studies, designed to test the mode of drug action, revealed a lack of effect on fertilization, ovulation, and implantation (248). The sterility effects of *Pisum sativum* may be due to m-xylohydroquinone as this compound interferes with progesterone (249), and the sterility action of subterranean clover seems estrogenic in nature (250).

*Pregnancy.*—The gestation period of wood rats is 35 to 42 days (251) and of American vampire bats, at least five months (252). Gestation times are influenced by breed differences but probably not by litter size (253). A fetal sex effect on gestation length is acknowledged, and denied (254, 255). Unlike other mammals, the giant fruit bat develops a progestational endometrium only at the implantation site (256).

Diagnosis of pregnancy and factors influencing the accuracy thereof continue to be explored (257). The Richardson test (free estrone) apparently

is too inaccurate for general use (258). Pregnanediol excretion signifying pregnancy is well summarized (259) with subnormal levels possibly signifying trouble. However, labor may be induced by aspirating amniotic fluid and replacing it with saline, but pregnanediol excretion does not decrease. Apparently a slow progressive injury increases fetal membrane permeability (260).

Toxemia of pregnancy is associated with subnormal serum cystine, a placenta with 55 per cent inferior villi and increased histamine (261, 262, 263), as well as an above normal excretion of corticosteroids with a poorly water soluble component (264) or desoxycorticosteroids (265). Salt and DCA in pregnant rabbits induce some aspects of human toxemia (266). Toxemia is high in diabetics and many pregnant diabetics exhibit exacerbation of the disease at the third and seventh month with high fetal loss (267).

A histochemical study of the bovine placenta has been reported (268) and the RNA/DNA composition of mouse and human placentae determined (269, 270). The mouse nucleic acid ratio reaches a maximum on the eleventh day and later declines. Chemical extraction of the placenta yields progesterone (271, 272), ACTH (273), adrenal steroids (274, 275), estrogens (276), and lactogenic factors (277).

Placental transfer of isotopic Ca and P permits bone studies (278, 279) and  $\text{Na}^{24}$  appears in human amniotic fluid in 6 min. (280). Ascorbic acid appears to facilitate the transfer of iron (281). Singular importance should be assigned to the placental transfer of digitalin (Digitoxin) by morphologically similar guinea pig and rat placentae, the former transferring 22 per cent, the latter 0.6 per cent in 1 hr. (282).

Fetal growth in multiple human pregnancies is at the singleton rate for 26 weeks and thereafter some individual but not total growth retardation occurs, possibly as a result of crowding (283). Fetal growth and development of the hamster have been recorded (284). Cortisone during pregnancy induces cleft palate in fetal mice and invites fetal degeneration in pregnant rabbits with sensitivity increasing in late pregnancy (285). ACTH did not affect progesterone-maintained pregnancy in spayed rabbits but did harm normal pregnancy, suggesting an ovarian disturbance (286). Cortisone may or may not influence Rh antibodies but may favorably aid the pregnancy (287, 288, 289). Fetal x-irradiation is followed by ocular abnormalities (290). In chicks, rumpleness, cleft palate, micromelia, etc., follow injection of various agents (291), including insulin, boric acid, and pilocarpine, possibly due to depletion of co-enzyme (292).

*Relaxin*.—The isolation and chemical properties, as well as morphological and biochemical effects of relaxin, reveal a variety of results (293). Electrometric changes follow palpable symphysis relaxation in the guinea pig (294). Pubic relaxation, seen with x-ray, occurs in estrus and during pregnancy in mice (295) and may provide an assay method in estrogen-primed mice (296). Estrogen priming permits response to relaxin in monkeys (297).



The ovarian extract may potentiate estrogen for mammary gland growth (298) in guinea pigs and rabbits but does not influence rats (299). Relaxin does not inhibit uterine responses to pitocin or acetylcholine but does negate spontaneous uterine contractions (300). Furthermore, these extracts will enhance and inhibit decidual formation, but the enhancing action appears not to be caused by relaxin (293). Other actions of ovarian extracts containing relaxin, although possibly nonspecific, are the duplication of the anemia of pregnancy (301) and the relaxation of the urinary tract (302).

*Mammary gland.*—Reviews concerning fat metabolism in the mammary gland (303) and the use of thyroid for increasing milk production have appeared with the question of economy still in the balance for thyroid feeding (304). Milk components have received considerable attention, and the estrogen (mostly conjugated) content of bovine colostrum is essentially as active as in man (305). The intramammary blood flow varies with the menstrual cycle, being low in the follicular and maximal in the secretory phase, with further increase in pregnancy (306). Suppression of postpartum lactation by estrogen remains questionable (307, 308).

Mammary gland response to prolactin exerts its full effect as the corpus luteum of pregnancy wanes (309) and the gland increases utilization of the hormone (310). A rough bioassay for prolactin is based on negating constant estrus in rats (311). Growth of the mammary gland results in a continuous increase of RNA throughout pregnancy and lactation (312) and a loss of stainable iron (313). Hypophysectomy during pregnancy does not prevent development of monkey mammary tissue, and substitution therapy did not sustain milk after parturition (314). Estrogen-induced glands may lack epithelial surface area (315), and this steroid may inhibit fetal gland development (316). During lactation, adrenal cortex to medulla weight ratios increase (317), and substitution therapy in adrenalectomy requires both DCA and cortisone (318). Large doses of DCA cause some duct growth, but the gland does not respond to progesterone (319).

*Milk "ejection" hormone.*—The most effective posterior pituitary fraction for milk ejection is oxytocin, although purified vasopressin proved one-fifth as active (320, 321). Within the gland, beta-hypophamine (Pitressin) and alpha-hypophamine (pitocin) increase intramammary pressure to the same degree, but pitocin more effectively ejects residual milk (322). Furthermore, an increase in milk per day may follow oxytocin injections, but daily variation in milk and fat yield continues (323). Using milk yield and duration of flow in lactating sows as a test for milk ejection activity, pituitary glands from monotremes, marsupials, and placental mammals of both sexes proved active (324). Lesions in the supraopticohypophyseal tract decrease milk yield in nursing rabbits, and gland evacuation is incomplete, but the gland responds to oxytocin (325). Other neurohypophyseal areas have been studied for hormone activity. The stalk contains one-tenth the activity of the posterior lobe while the median eminence is inactive (326). Emotional disturb-

ances influence milk yield and implicate the adrenal. Epinephrine can block the milk ejection response to pitocin in both rabbits and sows (327, 328).

#### NUTRITION AND REPRODUCTION

Functional integrity of a reproductive system requires proper nutrition (329). Sexual maturity is prevented in male rats by a protein-free diet (330), and testis recovery from estrogen inhibition is retarded by protein deprivation (331). The accessory organs quickly atrophy when food intake is subnormal, but the rate of decrease is slowed by addition of protein to the diet (332), these organs remaining responsive to androgen (333). Estrus is prevented by inadequate protein or restricted calories, and reduced calories delay reproductive senescence, but lactation in these mice is usually deficient (334). Feeding a protein-free diet from the day of breeding causes 90 per cent fetal death in rats during the first 10 days, but this induced hormonal deficiency can be circumvented with estrone and progesterone, which maintain normal pregnancies (335). Starvation of short duration is adequate to alter ovarian function and interfere with deciduoma formation (336) so that high protein diets may be more desirable in early pregnancy (337).

During 15 days of pregnancy a rat may gain 50 gm. Since the fetuses and placentae are small, most of the weight gain is maternal, possibly as a reserve for rapid late fetal growth. Feeding a protein-free diet or restricting food intake in the last trimester markedly influences maternal weight but does not alter fetal or placental weights. Maternal weight gain is abolished by fetus and placenta removals but not by fetus removal alone. Furthermore, this placental effect on maternal weight gain is apparent in the absence of the hypophysis, adrenals, and ovaries, but not when both ovaries and adrenals are extirpated in pregnancy. A sharp increase in liver RNA occurs in late pregnancy despite a protein-free diet. Fetus removal has only a slight effect on excess RNA accumulation, but placental removal abolishes it. Hypophysectomy reduces RNA excess, but the ovaries and adrenals seem not involved. A placental secretion or estrogen or both appear to be the major factors in this excess RNA accumulation in liver, most prominently observed in mice and rats, less readily in guinea pigs, and not seen in cats. Adrenal-ectomy, hypophysectomy, or a protein-free diet do not influence fetal or placental weight during the last third of rat pregnancy, but fetus removal alone retards placental growth (338, 339, 340). Liver fat also increases by three-fold during rat pregnancy regardless of diet or hormonal supplementation. Lack of lipotropic agents does not alter pregnancy or induce fetal liver fat but does impair lactation (341).

Fetal resorption in pyridoxine-deficient rats can be prevented by supplemental steroids, but hypophyseal extracts are only slightly effective (342). Nevertheless pituitary dysfunction may be involved as FSH content of the gland increases sharply in pyridoxine-deficient rats (343). Vitamin E deficiency in birds decreases pituitary gonadotrophins and testis function (344).

The folic acid antagonist, aminopterin, known to block estrogenic activity, will also counteract progesterone in deciduoma formation, but increased steroid levels may reverse the effect (345). Improved nutrition aided by unknown liver factors provides improved responses to androgen in severe oligospermia (346).

A 23 per cent fat diet decreases fertility in rats (347), whereas a fat-free diet invokes irregular estrus cycles and pituitary changes (348). Rats bred on a fat-free diet usually deliver dead young, corn oil serving as a preventative (349). Steroid usefulness in farm animals to increase weight gain and food efficiency continues to hold promise but can not be discussed.

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# THE PHYSIOLOGICAL DISTURBANCES PRODUCED BY ENDOTOXINS<sup>1</sup>

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## INTRODUCTION

The term endotoxin will be used in this review to designate, as a class, the relatively homogeneous group of toxic substances which exist as phosphorus-containing, polysaccharide-protein-lipid complexes in the intact cells of a wide variety of gram-negative microorganisms, or are liberated into culture media during autolysis of the bacteria.

The use of different descriptive terms for these substances by workers in different fields has given rise to the misleading impression that gram-negative bacteria produce a congeries of toxic materials, all differing in their properties as well as their names. The endotoxins of various microorganisms, although consisting of basically similar material, are variously known as toxic antigens, somatic antigens, polysaccharide toxins, tumor-necrotizing toxins, Boivin antigens or Boivin gluco-lipid toxins, or Schwartzman-active toxins. In the physiological literature they are commonly referred to as bacterial pyrogens, since this property of the endotoxins has attracted the interest of physiologists for many years. Adding somewhat to the confusion, the literature dealing with endotoxins contains numerous references to the materials by the name of the parent microorganism, and such terms as "dysentery toxin," "cholera toxin," etc. may be interpreted as indicating that the endotoxin is in some way implicated in the specific pathogenic properties of the bacterial source.

Because of the multiplicity of gram-negative bacteria which contain endotoxin, the basic resemblance between the materials is not readily appreciated. They are extractable from numerous unrelated species by similar methods, and when obtained in isolated form they appear to be similar in chemical structure and properties. They produce, in experimental animals, a syndrome of stereotyped physiological and pathological reactions, and, although different preparations may differ in potency, the effects of different endotoxins are qualitatively indistinguishable. These effects, which comprise the main subject of this review, include the following: (a) a profound vasomotor disturbance terminating in shock, characterized by intense, generalized arteriolar constriction, (b) a metabolic disturbance consisting of hyperglycemia followed by hypoglycemia, abrupt depletion of liver glycogen, and excessive amounts of lactic acid in the blood and tissues, (c) high fever, sometimes followed by hypothermia, (d) extreme polymorphonuclear leucopenia, followed by leucocytosis, (e) the production of hemorrhagic necrosis

<sup>1</sup> The survey of literature pertaining to the review was completed in October, 1953.

in the substance of rapidly growing tumors, and (f) with sublethal doses, the rapid appearance of a state of resistance against the same and other endotoxins. In addition, the endotoxins produce the local and generalized Schwartzman reactions, characterized by hemorrhagic necrosis in the skin and bilateral cortical necrosis of the kidneys, when two properly spaced injections of sublethal amounts are administered.

This review is concerned with the information which is available concerning the mechanisms underlying these apparently diverse effects of endotoxin and, more particularly, with a consideration of certain areas in which the effects may share common physiological mechanisms. A detailed consideration of all aspects of bacterial endotoxins is impossible to accomplish in a single review. The reader is referred to recent reviews by others which cover other areas of the problem (1 to 6).

#### THE GENERAL PROPERTIES OF ENDOTOXIN

*Toxic manifestations in animals.*—Endotoxins have been shown to cause manifestations of toxicity in numerous animal species, with a considerable variation in individual species susceptibility. The laboratory animals most studied have been mice, rats, guinea pigs, rabbits, cats, and dogs; of these the last two seem to be the least susceptible. With lethal doses of endotoxin, the grossly evident manifestations of intoxication are as follows: There is invariably a latent period, lasting 1 hr. or longer, during which the animals appear to be well. They then become less active, are disinclined to feed, and show increasing generalized weakness. During the next few hours they become ataxic and finally unable to stand. Fever appears after 3 or 4 hr.; in mice, hypothermia occurs instead of fever, and other animals may develop hypothermia in the terminal stages of intoxication. Respiratory distress, indicated by rapid, labored breathing and sometimes blood-tinged foam at the nostrils, is a conspicuous symptom. The dog and cat develop vomiting and retching, and all species have profuse fluid diarrhea. In the agonal stage, the animals lie completely immobilized and unresponsive to stimuli, and there may be generalized convulsive seizures. Death occurs after periods which range from 4 to 24 hr. and depend on the size of the dose of endotoxin.

The route of injection of endotoxin is of importance in certain species. In the rabbit, massive doses of endotoxin injected into the skin fail to cause systemic intoxication, while much smaller amounts are lethal when given by intravenous, intraperitoneal, or intracerebral routes (5, 7). In mice, subcutaneously injected endotoxin causes death.

Considering the violence of the systemic reaction to endotoxins, there is a paucity of anatomical changes in the tissues of animals which die after one injection of endotoxin. In the rabbit, there may be small punctate hemorrhages in the thymus, abdominal lymph nodes, lungs, and intestinal walls; the kidneys of rabbits do not show gross or microscopic lesions after a single lethal injection of endotoxin. Small areas of acute cellular necrosis sometimes occur in the liver, spleen, lymph nodes, and myocardium, and small thrombi



attached to the walls of veins in the liver and other organs are sometimes encountered (5, 8).

Some of the reports dealing with the pathological effects of endotoxin describe more extensive hemorrhagic lesions in visceral organs following repeated injections of endotoxin. In the rabbit, a second intravenous injection consistently produces an altogether different reaction from that observed after one dose, and this does not appear to be a function of the simple additive effect of more endotoxin. With two small doses, insufficient to produce any effect if combined and given in one injection, the second is followed by a new kind of lethal reaction in which extensive lesions of hemorrhagic necrosis occur in many organs; the kidney lesion which characterizes the event is bilateral cortical necrosis (5, 7, 9). This is the generalized Shwartzman reaction, which will be considered in a later section.

*Bacterial sources of endotoxin.*—A great many gram-negative bacterial species have been shown to contain endotoxin (2, 5, 10), but systematic studies of the material have been confined to a representative few sources. Most of the investigations considered in the present review were conducted with endotoxin from one or more of the following species: *S. typhosa*, *E. coli*, *B. proteus*, *S. marcescens*, *Ps. aeruginosa*, *Vibrio cholerae*, *S. aertrycke*, *S. paratyphi*, *Sh. paradysenteriae*, and meningococci.

Considerable variation exists in the amount of endotoxin present in different bacterial species, and there is also some difference between strains of the same species as well as variants of the same strain. For example, Tal (11) showed that endotoxin was contained in the S-variants but not in the R-variants of a strain of *Sh. dysenteriae*.

*Chemical properties.*—The present status of information concerning the chemical nature of endotoxins is discussed in a recent review by Burrows (2). A high degree of chemical purification of endotoxins has been accomplished by several investigators, without loss of biological activity (2, 12). The material can be extracted from dried bacterial cells by trichloroacetic acid [as in the procedure originally developed by Boivin and his associates (13)], or by phenol, pyridine, or diethylene glycol, and freed from other constituents by fractional precipitation with alcohol or acetone. The endotoxin is resistant to trypsin, and labile to mild acid hydrolysis.

Highly purified materials with the properties of a protein-acetyl-polysaccharide-lipid complex were prepared from dysentery bacilli by Goebel *et al.* (14, 15). The toxicity for mice was associated with a phosphorus-containing component which retained toxicity when combined with the protein or polysaccharide components. The lipid component did not appear to be involved in toxicity.

Relatively purified toxic components from other gram-negative bacteria appear to have similar constituents and make up a more or less homogeneous group of toxic substances existing as protein-polysaccharide-lipid complexes. The lipid component does not exhibit pharmacological or immunological activity. The esterified polysaccharide contributes immunological specificity

to the complex. The protein is closely bound to the polysaccharide, and when separated is toxic if still in combination with a phosphorus-containing constituent; the latter also seems to confer toxicity on the otherwise non-toxic polysaccharide (15).

In crude preparations of endotoxin, as in culture filtrates, thermostability characterizes the entire group and distinguishes them from most true exotoxins. Toxicity remains after the material has been heated at 100°C. The endotoxins in culture filtrates are sometimes unpredictably unstable, losing activity after prolonged storage, freezing, or as the result of mild acidification. The existence of an enzyme in *S. typhimurium* and *S. enteritidis* which is capable of destroying the endotoxins of these bacteria was reported by Boivin & Mesrobian (16); unpredictable variations in the endotoxin activity of other microorganisms might be brought about in this way.

Iodination of purified *S. marsecens* endotoxin with radioactive iodine was accomplished by Seligman & Sack, with apparent retention of the tumornecrotizing activity of the material (17).

*Immunological properties.*—The endotoxins of most gram-negative bacteria are effective antigens and have been widely used as "somatic antigens" for immunological identification and classification. Antisera prepared by animal immunization are active in precipitation, agglutination, and complement-fixation tests. The endotoxin functions as a complete antigen when isolated from trichloroacetic acid extracts and has been shown by Boivin (18) to be indistinguishable from the somatic antigen. Antigenicity is dependent upon the association between protein and polysaccharide; Morgan & Partridge (19, 20) found that when the two were separated antigenicity disappeared, and was restored when they were recombined. The isolated protein had the property of combining with other, nonantigenic polysaccharides, forming new antigenic complexes with specificity determined by the new polysaccharides.

Curiously, neutralization of the toxic properties by specific antibody has been reported not to occur, or to occur only with very large amounts of antibody (21, 22). For example, Morgan (22) combined a preparation of typhoid endotoxin with specific serum and separated the resulting precipitate by centrifugation; the supernatant fluid was devoid of toxicity, and the immunologically precipitated material retained the toxicity of the original material. Others have observed that actively or passively immunized animals are protected to a slight extent, if at all, against endotoxin.

Confusion concerning the immunological properties of endotoxin existed in earlier investigations because of misinterpretation of the phenomenon of acquired resistance, which is brought about during the course of repeated injections of small amounts of endotoxin. The nonspecificity of this state of resistance became clear when it was shown that animals which developed tolerance for one endotoxin were equally resistant to the effects of other immunologically unrelated endotoxins (23).

## THE EFFECTS OF ENDOTOXIN ON BLOOD VESSEL FUNCTIONS

This section is concerned with the functional alterations of blood vessels which accompany systemic intoxication of endotoxins, and with certain related physiological changes. The necrotizing vascular lesions which comprise the Shwartzman reaction will be considered in a later section.

A major portion of the available information regarding the vascular effects of endotoxins has been contributed by a group of French investigators. Since 1941, Delaunay, Boquet and their associates have conducted a series of illuminating experiments demonstrating that endotoxins produce a profound sympathomimetic reaction in experimental animals and indicating that other important physiological disturbances may be the result of this vascular reaction. Detailed summaries of the work have been published in recent years by Delaunay *et al.* (6, 24, 25).

The endotoxins employed by Delaunay were prepared by the Boivin method from cultures of typhoid and paratyphoid bacilli. The experiments were conducted with rabbits, guinea pigs, and mice. At the outset, direct microscopic observations were made of the exposed vascular bed in the mesentery and ear (26) at various times after an intravenous or intraperitoneal injection of endotoxin.

Within a period of 5 to 15 min. after injection, they observed a brief acceleration of blood flow, which was soon followed by a sudden, intense, generalized constriction of all arterioles. The vessels were converted into thin, thread-like strands, or disappeared completely from vision. After approximately 5 min. the arterioles dilated again, but a few minutes later a new prolonged period of constriction occurred. These waves of arteriolar constriction and dilatation continued for several hours, or until death of the animal; in lethal reactions the periods of vasodilatation gradually became longer and more extreme, with marked slowing of blood flow shortly before death.

During the cycles of constriction, the blood flow through the capillaries slowed and sometimes reversed in direction. The capillaries themselves were not observed to constrict. The venules were usually of normal calibre. Boquet & Izard (27) observed an abrupt fall in the surface temperature of the rabbit ear at the time of appearance of vasoconstriction; the temperature remained at levels as low as 10°C. below normal throughout the entire period of the reaction.

The constriction of arterioles and the fall in skin temperature were not prevented by denervation of the ear. On the contrary, the temperature response was much exaggerated in ears which had been denervated by unilateral sympathectomy several days previously (28). The arterial blood pressure remained within normal limits throughout most of the period of vasoconstriction, and decreased sharply a short time before death (29). *N*-(2-chloroethyl) dibenzylamine (Dibenamine) prevented the occurrence of arteriolar constriction, as well as the fall in skin temperature (27), although

it did not prevent death of the animals. The observations suggested that the effects of endotoxin on the vascular system involved a potent, long-lasting adrenergic mechanism, and the authors explored the possibility that other physiological effects of endotoxin might have a similar basis. Hyperglycemia, which occurred regularly in rabbits during the first few hours after injection of endotoxin (see pp. 475-76) is known to be produced by epinephrine. In the latter circumstance, it may be prevented by the sympatholytic action of dihydroergotamine (30), although not by Dibenamine (31). Boquet & Izard (32) obtained analogous results in hyperglycemia induced by endotoxin, i.e., prevention by dihydroergotamine and no alteration with Dibenamine.

Additional points of similarity between the actions of epinephrine and endotoxin, cited by Delaunay *et al.* (6), include leucocytosis, which is caused by both (although the conspicuous early leucopenia following endotoxin does not occur with epinephrine), and an interference with the migration of leucocytes from capillaries into inflamed or irritated tissues (diapedesis) (33). The similarity between the diapedesis-inhibiting action of endotoxin and epinephrine has also been noted by Miles & Niven (34). According to Delaunay, Dibenamine prevented the effect of epinephrine but not that of endotoxin. The possibility exists that at least part of the apparent interference with leucocyte migration following endotoxin may be a function of the extreme leucopenia in intoxicated animals, rather than an effect on blood vessels.

The role of arteriolar spasm and tissue anoxia in the pathological manifestations of endotoxin was studied by Delaunay and co-workers (6). Animals dying after large doses of endotoxin exhibited microscopic lesions of cellular necrosis in lymph nodes, spleen, and liver, and also small areas of hemorrhage and congestion in the walls of the stomach and intestinal tract. Comparable lesions were observed in animals injected with lethal doses of epinephrine by Delaunay, and by Penner & Bernheim (35). Moreover, the subcutaneous injection of healthy lymph node cell suspensions in company with epinephrine resulted in acute necrosis of the injected cells, while control suspensions without epinephrine remained normal in appearance (25).

The striking resemblances between the manifestations of endotoxin intoxication and traumatic shock have been emphasized by Delaunay and others. Comparable changes in the behavior and calibre of small vessels have been observed in shocked animals by several groups of workers (36, 37). The metabolic abnormalities which follow endotoxin, including hyperglycemia, early disappearance of liver glycogen (38, 39), elevated blood lactate and pyruvate (with lactate rising disproportionately higher than pyruvate) (39), and an increase in blood inorganic phosphate (39) are events which also occur in traumatic shock (40). Inhibition of diapedesis and a concomitant enhancement of subcutaneous tissue infections have been shown to occur in both situations (33, 34). Leucopenia is less commonly observed in the early stages of shock, but high degrees of leucocytosis occur late in both. Fever,

although more conspicuous in the endotoxin reaction, may also occur in shock (41). Comparable tissue lesions, consisting chiefly of necrosis in lymphoid tissues and gastrointestinal mural hemorrhages, occur in both (6).

The possibility that certain forms of shock in human beings may result from the action of bacterial toxins has been emphasized by Fine *et al.* (42) on the basis of experimental evidence that irreversible traumatic and hemorrhagic shock may be accompanied by absorption of bacterial products from injured or anoxic tissues. Typical shock has been observed following transfusion with contaminated blood or other fluids (43). An additional, curious similarity between shock and endotoxin poisoning lies in the demonstrated ability of experimental animals to develop resistance after repeated exposure to sublethal stimuli; the acquired resistance to drumshock in rats (44) bears at least a superficial resemblance to the phenomenon of acquired resistance to endotoxins.

*The mechanism of the vascular effects of endotoxin.*—Although there is much to suggest that an adrenergic mechanism is involved in the action of endotoxin, the nature of the mechanism remains undetermined. Activation of the adrenal medulla and overproduction of adrenin have been suggested as contributing factors, and histological evidence that depletion of adrenal chromaffin substance occurs after endotoxin (45) lends additional support. The likelihood that some humoral mechanism mediates the arteriolar constriction effect is suggested by Boquet's observations with denervated ear vessels, cited above.

The implication of an autonomic neural mechanism in the action of endotoxin was proposed in 1935 by Reilly and associates (46). The theories proposed by this group of French investigators, based on experiments indicating a direct action of endotoxin on sympathetic nerve fibers, have received much attention in the French literature and general acceptance in many quarters. A set of general hypotheses concerning the mechanism of tissue damage in various disease states is based on what is frequently referred to as the "Reilly phenomenon" (47). The work of Reilly has received little attention in American reviews of the endotoxin problem and requires mention. According to Reilly, there is a selective affinity of endotoxin for sympathetic nervous system tissues, and the reaction of lymphoid tissues to the presence of endotoxin is mediated through an effect on sympathetic neural connections. The experimental basis for this view is the reported observation that an injection of small quantities of typhoid or paratyphoid endotoxin in the immediate vicinity of the splanchnic nerve resulted in hemorrhage and necrosis in the stomach and intestines, followed by shock and death (46). The same or larger amounts of endotoxin were without effect when injected by intracardiac or other routes, implying a direct action on the splanchnic nerve. In addition, Reilly reported that similar effects were produced by mechanical or chemical injury to the nerve, and that faradic stimulation caused marked changes in the defense response of mesenteric lymph nodes to locally injected typhoid bacilli. The original endotoxin experiments

were conducted with relatively crude bacterial preparations; in 1940 they were repeated by Gastinel & Reilly (48) with a "gluco-lipid" endotoxin obtained by the Boivin method, and the results were reported to be the same. Appraisal of these observations, and of the numerous speculative theories concerning the role of the sympathetic nervous system in infection and immunity proposed in subsequent papers of Reilly and his group (49), must await experimental confirmation and extension of the work.

*The effect of endotoxin on the central nervous system.*—The effect of endotoxin injected intracerebrally has been studied by several workers, with inconclusive results. According to Schwartzman (5), an intracerebral injection is as effective as one given intravenously for provoking the local Schwartzman reaction; the reviewer has observed provocation of the generalized reaction in rabbits which received the first injection of meningococcal endotoxin in the brain, and the second injection by vein (50). Apparently endotoxin is rapidly absorbed from the brain into the blood stream, in contrast to its fixation in skin (51). According to Reilly *et al.* (46), rabbits were much more susceptible to the lethal effect of typhoid endotoxin given intracerebrally than when injected intravenously.

Penner & Klein (52) reported the results of an ingenious experiment which indicated that certain systemic effects of dysentery endotoxin in dogs were mediated through a direct effect on the brain. These authors succeeded in transposing the carotid and jugular circulations in six pairs of dogs, after having eliminated the vertebral circulation in previous operations. The result was a cross-circulatory arrangement in which the major portion of the blood supply of each dog's head was received from the systemic circulation of the animal's partner. The animals were maintained under pentobarbital sodium anaesthesia, and one member of each pair was given an injection of endotoxin in the femoral vein. The dose of endotoxin was sufficient to produce severe systemic reactions in normal dogs. Observations were made during a period of 4 to 6 hr. after the injection.

The results obtained by Penner & Klein are of extreme interest. In each pair of dogs, one member exhibited the characteristic response of this species to endotoxin, including leucopenia, hyperglycemia, hemoconcentration, and acute lesions of congestion, edema and hemorrhage in the walls of the stomach, intestines, and gall bladder. In each instance, the dog in which these changes occurred was the one which did not receive the femoral vein injection of endotoxin. Presumably, the only possible exposure to endotoxin in these animals was by way of the cerebral circulation derived from the opposite animal. In contrast, the dogs which received the full dose of endotoxin in their systemic circulation, but not in the cerebral circulation, showed none of the systemic effects of endotoxin. The differences observed in the leucocyte counts in each pair of dogs were particularly striking; for example one animal showed a fall in the white count from 12,200 to 1,700 one hour after toxin, and the cells remained at this level during the next two hours. The partner animal, which had received the endotoxin injection, maintained



a count in the neighborhood of 12,000 throughout the period of observation (furnishing, incidentally, additional evidence for the authors' view that little if any circulatory communication existed between head and body of these animals).

The experiments of Penner & Klein appear to open up a new and potentially fruitful approach to the problem of the mechanism of action of endotoxin. There is no alternative explanation that seems as reasonable as their own, which is that, in the dog, dysentery endotoxin produces several of its most important systemic effects by an action on the central nervous system. They suggest that a possible site of action within the brain may be in the region of the tuber cinereum and adjacent hypothalamus; penetration of toxin here might result in the firing of a diffuse sympathomimetic discharge.

*Other vascular effects.*—Tachycardia and diminished force of heart beat was reported to occur in the guinea pig after injection of endotoxin by Delaunay *et al.* (6). Electrocardiographic abnormalities were observed in rabbits after *S. marcescens* endotoxin by Leese and co-workers (53). Perfusion of the turtle heart with purified *S. marcescens* endotoxin resulted in evidences of direct injury, with conduction block and extreme cardiac dilatation (54).

A marked increase in renal blood flow, persisting for many hours and amounting to 35 to 60 per cent above normal, was observed by Smith in humans and animals following pyrogenic doses of endotoxin (55). The increased flow was attributed to dilatation of the efferent glomerular arterioles. The effect was not prevented by antipyretic drugs but, according to Takos & Moe (56), it was abolished by dihydroergotamine.

A destructive lesion in the kidneys, consisting of bilateral cortical necrosis, occurs in rabbits after two intravenous injections of endotoxin. The lesion is not produced by a single injection, regardless of the dosage (see p. 482).

#### THE EFFECTS OF ENDOTOXIN ON CARBOHYDRATE METABOLISM

Conspicuous manifestations of a disturbance in carbohydrate metabolism have been described by many investigators (2), and there is general agreement that the following events occur with regularity during intoxication by endotoxin. The blood sugar becomes elevated within 1 or 2 hr. after injection, and hyperglycemia persists for several hours. In severely poisoned animals this is followed by extreme hypoglycemia during the terminal stages. The liver glycogen becomes greatly reduced within 1 or 2 hr. after injection (39). The lactate content of the blood and tissues becomes much elevated, and there may be a concomitant increase and subsequent decrease in pyruvate (39).

Menten & Manning (57) observed hyperglycemia in guinea pigs and rabbits during spontaneous salmonella infections. The production of hyperglycemia by injecting suspensions of killed gram-negative bacteria was reported in 1925 by Zwecker & Goodell (58) and studied in detail by Evans & Zwecker (59), who found that the effect was completely prevented by er-



gotamine and reversed by insulin. Postulating that hyperglycemia was the results of central stimulation of the adrenals, they injected suspensions of *E. coli* into adrenalectomized rabbits and observed, instead of hyperglycemia, a profound fall in blood sugar levels accompanied by convulsions and death of the animals.

Similar events have since been described by other workers, employing highly purified preparations of endotoxin from various bacterial sources. In rabbits (32) the increase in blood sugar may reach levels higher than 400 mg. per cent within 2 hr. after an injection of typhoid endotoxin, and in dogs (52) an increase to more than double the normal level may be produced within 1 or 2 hr. Boquet & Izard (32) recently reported that the hyperglycemic response to typhoid endotoxin in rabbits could be prevented by dihydroergotamine but not by Dibenamine. It was of interest that the mortality was highest in the animals in which hyperglycemia was prevented.

Hyperglycemia occurs in other species, including mice, rats, guinea pigs, and cats, following injections of killed gram-negative bacteria or endotoxins. Feldman & Gellhorn observed hypoglycemia in adrenalectomized rats injected with typhoid vaccine (60) and also noted that vagotomy, which did not prevent hyperglycemia, resulted in a longer-lasting elevation of blood sugar and fever than that in normal animals.

The marked increase in the lactate content of blood and tissues was studied by Kun & Miller (39). In the later stages of intoxication, when hypoglycemia was present, the lactate continued to rise, but the concentration of pyruvate became much diminished. Almost complete depletion of the liver glycogen occurred regularly [this change has been used by Tal & Olitski (38) for biological assay of endotoxin activity]. Kun and associates demonstrated an inhibition of succinic dehydrogenase activity in muscle and liver from poisoned animals; cytochrome oxidase activity was not affected. It was suggested that the observed effects might be accounted for on the basis of tissue anoxia. An increased concentration of lactic acid occurs in skin areas injected 24 hr. previously with meningococcal or *S. marcescens* endotoxin, and sections of the skin continue to produce large amounts of lactic acid *in vitro* (61).

The mechanism by which endotoxins produced the observed metabolic abnormalities requires much further study. It is possible that some, if not all, of the effects are closely related to the adrenergic action on blood vessels described in the preceding section. Whether the metabolic changes represent direct effects of the vascular reaction as a manifestation of tissue anoxia, or are mediated through some other mechanism, they undoubtedly contribute to the general state of intoxication and may be of importance in the lethal outcome.

#### THE PYROGENIC EFFECT OF ENDOTOXIN

The unique property of gram-negative bacterial endotoxins to cause febrile reactions in animals and man has stimulated the interest of numerous

investigators for many years, and an enormous body of literature dealing with the subject has accumulated. A comprehensive review of the pyrogen problem was presented in 1950 by Bennett & Beeson (3). The present section will be limited to a brief consideration of relationships between the pyrogenic and other physiological effects of endotoxin.

It does not seem probable that the property of causing fever involves an independent constituent of endotoxin, separate from the material which produces other, more drastic effects. The point deserves mention in view of the increasingly widespread use of "purified pyrogens" in the treatment of disease. The febrile response is an extremely sensitive physiological indicator of endotoxin activity, and very much smaller doses are required than for the production of other reactions. It is probable that some of the materials which are said to be "pure" pyrogens, without other toxic properties, actually represent endotoxin weakened by denaturation.

No single mechanism adequately accounts for the febrile response to endotoxin, and it is possible that different mechanisms may operate in different species (for example, the mouse reaction to endotoxin by a fall in temperature instead of fever). The violent constriction of peripheral arterioles, associated with a fall in skin temperature (27), reduces greatly the area for heat loss and thus provides a mechanism for fever, provided that heat production by internal tissues is maintained. Grant (62), and Wells & Rall (63) reported that the pyrogenic effect of typhoid vaccine in rabbits and dogs can be largely accounted for by reduced loss of heat. The latter workers found that curarization did not diminish the febrile response in dogs, a point against increased heat production as a significant contributor to fever. On the other hand, adrenergic blocking agents, which inhibited peripheral vasoconstriction, reduced the degree and duration of fever. The situation differs in man. According to Dubois (64) peripheral vasoconstriction is of less importance, and overproduction of heat is a primary factor in fever.

Resistance to the pyrogenic effect of endotoxins develops in animals and man after repeated injections of small doses. This phenomenon, studied in detail by Beeson (23, 65), Morgan (66), and others does not involve any recognized immunological mechanism. It is entirely nonspecific, cannot be correlated with measurable antibody reactions, persists for a shorter time than is compatible with immune phenomena, and is completely eliminated by the injection of reticuloendothelial "blockading" agents such as Thorotrast<sup>a</sup> and trypan blue (65). Resistance to other actions of endotoxin will be discussed in a subsequent section.

A factor in plasma which accelerates and augments the pyrogenic effect of endotoxins has been studied by several workers (67, 78). The manner of its action has not been determined, nor has it been identified. Recently, the activity of the factor was compared in normal and pyrogen-resistant animals,

<sup>a</sup> Thorotrast is a trade name which refers to a thorium dioxide suspension containing 25 per cent ThO<sub>2</sub>.

by Grant & Whalen (68, 69). According to these workers, the plasma factor was diminished in the blood of resistant animals; it was suggested that this deficiency might play a role in resistance.

The role of the central and autonomic nervous systems in the production of fever by endotoxins has been much studied. Variable effects have been noted in animals subjected to hypothalamic injury (70). Chambers and associates (71) observed abolition of the febrile reaction following transection of the cervical cord, and Pinkston (72) demonstrated delay and inhibition of fever in completely sympathectomized cats. Feldman & Gellhorn (60) found that removal of the adrenal medulla changed the response from hyperthermia to hypothermia.

#### THE EFFECTS OF ENDOTOXIN ON LEUCOCYTES

It has long been known that the injection of pyrogenic bacterial products, in animals and man, is followed after some hours by leucocytosis; indeed, this was part of the rationale for the introduction of such materials in medicine.

A more constant reaction to endotoxins, and one which is equally important in its physiological implications, is the profound polymorphonuclear leucopenia which occurs within 1 hr. after injection and persists for 2 or 3 hr. This phenomenon was described in detail by Delaunay (73), in 1943, and was attributed to retention of the leucocytes in the capillaries of the lungs, liver, and spleen. Doan and associates (74) had previously suggested a similar explanation for the leucopenia following injections of a pyrogenic preparation of nucleinate.

A comparable fall in the number of circulating platelets after injections of gram-negative bacteria and their endotoxins has been observed by several investigators (75).

Neither leucopenia or thrombocytopenia are in any sense specific manifestations of endotoxin. Both have been observed in anaphylactic shock (76), and after intravenous injections of peptone, glycogen (77), and suspensions of various other colloidal and particulate materials. With suspensions of glycogen, extreme leucopenia can be produced without any of the evidences of intoxication which occur with endotoxins (77).

An *in vivo* chemotactic effect of endotoxin for leucocytes was described by Delaunay and co-workers (78). Typhoid endotoxin, in optimal concentrations, acted as an attracting stimulus for polymorphonuclear leucocytes in tissue. With the endotoxin employed, the maximum activity was exhibited by dilutions between 1 to 100 and 1 to 1000. It was of interest that stronger concentrations had less chemotactic effect. Contrary results were obtained by Morgan & Uphan (79), and by Martin & Chaudhuri (80), who reported *in vitro* inhibition of leucocyte migration by typhoid, meningococcus and *S. marcescens* endotoxins. No *in vitro* effect was observed by Berthrong & Cluff (81).

Delaunay's observations of the leucocyte response *in vivo* appear to have

more meaning than the failure of others to show chemotaxis *in vitro*. There have been many studies on the reaction of skin to an injection of endotoxin, and almost all have emphasized the extremely dense accumulations of polymorphonuclear leucocytes which occur in the tissue during the next 24 hr. (5). It is probable that this chemotactic effect may occur as a secondary response to altered tissue, rather than as a direct attraction of the leucocytes by endotoxin. But in any event, the end result indicates a potent capacity of endotoxin to cause local leucocyte infiltration in an injected area.

Martin and associates (82) developed a technique for *in vitro* studies of the metabolic functions of uninjured leucocytes involving the use of siliconized vessels and reported that endotoxin caused an increase in aerobic glycolysis in polymorphonuclear leucocytes, as well as the release from cells of a material resembling lysozyme (83).

Berthrong & Cluff (81) studied the migration of leucocytes from the buffy coat in centrifuged blood samples which were drawn at various intervals after an intravenous injection of endotoxin. Definite inhibition of migration was present in blood taken between 5 min. and 12 hr. after injection. The effect could not be reproduced by *in vitro* exposure of blood cells to endotoxin, and was not demonstrable in uncentrifuged blood. It may be analogous to the increased adhesiveness and tendency to clump which Stetson (77, 84) had shown to occur in rabbit leucocytes after injection of endotoxin. Cluff (85) reported that the inhibition of cell migration no longer occurred when nonspecific resistance to endotoxin was induced by the repeated administration of small doses.

Interference by endotoxin with diapedesis in capillaries, described by Delaunay *et al.* (33) may represent an indirect effect on leucocyte function (see p. 471). A similar type of inhibition was described by Miles & Niven (34) in animals subjected to shock by various other methods.

It is doubtful that the changes in the circulating levels of leucocytes and platelets contribute much to the acute systemic manifestations in animals dying from a single lethal dose of endotoxin. However, the participation of these cellular elements in the pathogenesis of the Schwartzman reaction is strongly indicated, as will be shown in a later section.

#### THE EFFECTS OF ENDOTOXIN ON MALIGNANT TUMORS

The apparently selective destructive effect of bacterial products on rapidly growing tumors have been recognized since the end of the last century. In recent years it has become evident that the effect represents one of the properties of gram-negative bacterial endotoxins. The earlier literature dealing with the subject has been reviewed and summarized by Nauts *et al.* (4).

Soon after Schwartzman's description of the local phenomenon of altered reactivity, Gratia & Linz (86) undertook a study of the effect of bacterial endotoxins in mice bearing experimental sarcomas. These workers, and later numerous others (5) found that within a few hours after an intravenous

injection of endotoxin, hemorrhagic necrosis occurred in the tumor, often with complete destruction of the entire growth. An endotoxin prepared from *S. marcescens*, purified by the method of Shear and co-workers (87), has been used in most of the recent investigations of this phenomenon; identical reactions have been observed with endotoxins from numerous other forms of bacteria (88). No adequate explanation is available for the selective vulnerability of tumors. Several workers have shown by tissue culture techniques that endotoxins are not cytotoxic for tumor cells *in vitro* (89).

It is of interest, and perhaps of meaning, that other tissues which are similarly vulnerable to the necrotizing effects of circulating endotoxin, and which undergo hemorrhagic necrosis a few hours after intravenous injection, are the decidual placenta (90), infected tissue sites (91), and skin tissue prepared for the local Shwartzman reaction by a previous intradermal injection of endotoxin. One property, which is shared in common by such tissues and tumors, is an increased capacity to form lactic acid aerobically (61, 92). It is conceivable that the pH changes associated with lactic acid accumulation in these tissues, when deprived of an adequate supply of blood, might lead to more drastic injury than in other tissues.

Algire and associates (93, 94) have emphasized the important role played by the vasomotor response to endotoxins. They made direct microscopic examinations of blood vessels in neoplastic tissues during the reaction to *S. marcescens* endotoxin and observed severe stasis of blood flow, arteriolar constriction, capillary thrombosis, and subsequent hemorrhage. They also demonstrated marked hypotension during the period of the tumor reaction. According to Beck *et al.* (95), hypotension, hypothermia, prostration, and death are more likely to occur in tumor-bearing mice than in normal animals after an injection of endotoxin.

#### INDUCED RESISTANCE TO ENDOTOXINS

The phenomenon of induced resistance, which develops in animals after a series of exposures to small amounts of endotoxin, has been shown to involve most of the physiological effects under discussion in this review. On the basis of present evidence, two generalizations can be stated: (a) When animals are made resistant to the endotoxin of one species of bacteria, they are resistant to other endotoxins. (b) When animals are made resistant to one effect of endotoxin, they are resistant to other effects.

The immunological nonspecificity of the phenomenon has been discussed in earlier sections. Its physiological scope is indicated by listing the actions of endotoxin which it has been shown to involve: the febrile response (23), tumor necrosis (96), inhibition of leucocyte migration (85), leucopenia (23), the local (97) and generalized (98) Shwartzman reactions, and the primary lethal effect of a single large dose (98).

Windle *et al.* (99) studied the histological alterations which occurred in resistant animals after prolonged treatment with endotoxin. The most conspicuous changes were in lymphoid organs and consisted of extensive hyper-

plasia of lymphocytes and macrophages. In addition, the spleen contained islands of hematopoietic tissue, resembling sections of bone marrow. The spleen and lymph nodes were markedly enlarged. The author noted that the changes were the opposite of those seen in cortisone-treated animals.

Beeson (97) learned that the state of resistance to the febrile response was accompanied by resistance to the local Schwartzman reaction, and both types of resistance disappeared within a few hours after an intravenous injection of Thorotrast or trypan blue. The suggestion was made that resistance represents a function of the reticuloendothelial system.

Morgan (100), having previously shown that human beings become resistant to the febrile effects of several purified endotoxins, tested the responses in patients during convalescence from different types of febrile disease. He noted greater than normal tolerance following typhoid and paratyphoid fever, but no alteration in patients recovering from bacillary dysentery, gonococcal arthritis, pneumococcal pneumonia, or tularemia.

In contrast with this observation, Bennett (101), in a well-controlled experiment, studied the effect of experimental bacterial infections on the subsequent response to bacterial pyrogens in rabbits, in an effort to determine whether the fever of infection is capable of inducing resistance. Using two groups of rabbits, with pneumococcus skin infection or *E. coli* peritonitis, he was unable to demonstrate any enhancement of resistance during convalescence. He interpreted the results as indicated that the fever of infection, in these circumstances, is based on a different mechanism from that involved in the action of pyrogenic endotoxin. The possibility that the infection itself might have interfered with a mechanism normally capable of inducing resistance (such as the reticuloendothelial system) was controlled by his demonstration that rabbits with peritonitis which were simultaneously treated with pyrogens developed resistance in the normal manner.

#### FACTORS AFFECTING THE LETHAL ACTION OF ENDOTOXIN

It is clear that some of the individual physiological disturbances produced by endotoxin are, in themselves sufficiently injurious to cause death, but it is by no means certain that any or all of them are the actual cause of death in endotoxin-poisoned animals. Other undiscovered mechanisms may prove to be of more central importance.

This section is not concerned with the manner in which death occurs, but with a number of factors which have been shown to influence the lethal action of toxin.

*The influence of age.*—Zahl, Hutner & Cooper (102) compared the susceptibility to the lethal effect of endotoxin in rats of different ages. The younger animals seemed more resistant than adults when the lethal dose was calculated in terms of body weight, but the total dose which caused death was approximately the same. The results were assumed to be consistent with the view that endotoxin exerted its effect at a single vulnerable site, rather than in all cells of the body. In contrast, rabbits of different ages were found

by Smith & Thomas (103) to be remarkably different in susceptibility. Small recently weaned rabbits weighing 0.5 kilos were capable of withstanding doses of meningococcal endotoxin more than fifty times greater than the amount which caused death within less than 18 hr. in fully grown adults weighing 3.0 kilos. An injection of colloidal iron saccharate, a few hours before endotoxin, which had been shown to enhance greatly the lethal effect of endotoxin (104), eliminated the difference in susceptibility of the two groups. A comparable difference between large and small rabbits was noted in the duration and extent of the febrile response. The possibility that young animals may be better endowed with a mechanism related to induced resistance requires further study.

*The influence of species.*—Major differences exist between animal species in their susceptibility to endotoxins. For example, mice, rabbits, and guinea pigs are much more susceptible to all toxic effects than are dogs and monkeys.

*The influence of bacterial infection.*—Rabbits with systemic infections by Group A hemolytic streptococci were found to be highly susceptible to the lethal action of meningococcal endotoxin when toxin was injected a day or more after streptococci. Death occurred in many animals, with bilateral renal cortical necrosis and lesions of the coronary arteries. When the order of injections was reversed, and endotoxin given one day prior to streptococci, no deaths occurred and no lesions developed (91).

*The effect of thorotrast and related substances.*—Beeson (97) noted, in the course of experiments concerned with acquired resistance to endotoxins, that injections of Thorotrast prior to endotoxin caused enhancement of the lethal effect. Good & Thomas (105) observed an approximately thousand-fold increase in the capacity of meningococcal endotoxin to cause death in rabbits injected with Thorotrast before endotoxin; comparable enhancement was also produced by colloidal iron (104).

*The effect of adrenalectomy.*—The increased susceptibility of adrenalectomized animals to endotoxin has been mentioned in a previous section. The effect may be analogous to the well-documented hypersusceptibility to traumatic shock in such animals, in view of other similarities between shock and endotoxin-poisoning. Lewis & Page (106) showed that therapy with cortical extracts and cortisone allowed the survival of adrenalectomized rats after an injection of typhoid vaccine.

*The effect of cortisone.*—Various and conflicting reports have appeared concerning the effect of cortisone on the lethal effect of endotoxin. In mice, protection against brucella endotoxin was demonstrated by Spink (107). In rabbits, an antipyretic effect has been demonstrated against several endotoxins (108). Thomas & Good (51) found that cortisone-treated young rabbits developed bilateral cortical necrosis of the kidneys after a single injection of meningococcal endotoxin. In older, mature rabbits, the early lethal effect of endotoxin can be prevented by cortisone pre-treatment, although renal necrosis also occurs in these animals (50).

*Other substances.*—A component in crude penicillin preparations was



reported by Boor & Miller (119) to protect mice against the lethal effect of meningococcal endotoxin. Zahl and associates (120) observed protection against *Salmonella* endotoxin by certain sulfonamide compounds, and also by thiouracil, and suggested that the effect was mediated through depression of the thyroid. Smith & Humphrey (121) and Schwartzman & Schneerson (122) reported that large doses of salicylate suppressed the dermal Schwartzman reaction; the latter workers observed enhancement of the protective effect by the addition of pantothenate, indicating a synergistic action of the two compounds.

#### THE SHWARTZMAN REACTION

A comprehensive review of the recent literature concerning the Schwartzman reaction cannot be undertaken within the available space, and no attempt will be made to do so in this section. Instead, certain points of similarity and dissimilarity between the events which occur after a single injection of endotoxin and those involved in the Schwartzman reaction will be considered briefly.

In none of the physiological disturbances described thus far can it be established that endotoxin is exerting a direct effect on the tissues which appear to be the site of disturbance. Each manifestation seems to occur indirectly as the result of the operation of a mediating mechanism. None of the mediating mechanisms has been identified with certainty, although there is circumstantial evidence for the participation of nervous tissue centers in some of the reactions.

Although the Schwartzman reaction presents the appearance of a direct, necrotizing action of endotoxin on tissues, there is much experimental evidence which indicates that a series of indirect effects are responsible for the changes which occur during the development of the reaction. Some of the mediating mechanisms which seem to be in operation in the pathogenesis of the Schwartzman reaction have already been shown, in the preceding sections of this paper, to be themselves affected by endotoxin. It is conceivable that the joint, coordinated action of two or more of these mechanisms, as the result of the manner in which the two injections of endotoxin are timed, may account for the lesions of hemorrhagic necrosis which characterize the reaction. The participation of leucocytes in the local reaction may exemplify such a coincidence.

*The local Schwartzman reaction.*—This is produced in the rabbit by giving a "preparing" injection of endotoxin in the skin, and then, after an optimal period of 18 to 24 hr., a "provoking" injection of endotoxin by vein. Within 3 hr. after the latter injection, hemorrhagic necrosis occurs at the prepared skin site.

During the period of preparation, the most conspicuous change in the skin is the entry of great numbers of polymorphonuclear leucocytes into the tissue (109). By the end of 18 hr. these cells are crowded together in the interstitial spaces and concentrated in dense cuffs around blood vessels. The

vessels themselves show no histological evidence of damage to their walls, and there are no thrombi. There is a moderate degree of edema. The permeability of vessels in the area may be altered; it has been shown that intravenously injected trypan blue does not stain the prepared skin site, even when sufficient dye is injected to cause staining in all other skin areas (110). The lactic acid content of the prepared skin is approximately double that of normal skin, and the capacity to form lactic acid *in vitro* is increased ten-fold or more (61).

Several events which involve the circulating polymorphonuclear leucocytes occur in sequence during the period of provocation, after the intravenous injection of endotoxin. Stetson (77, 84) has presented evidence which indicates that these changes may constitute the final event which leads to necrosis and hemorrhage in the prepared skin. First, the leucocytes and platelets become aggregated in clumps of irregular sizes, which can be seen during the first hour after injection by direct microscopic examination of the small vessels in the ear, or demonstrated in samples of heparinized blood. Stetson (77) attributes the formation of these clumps of cells to an increased adhesiveness of the leucocytes.

The second major change in provocation is the occurrence of polymorphonuclear leucopenia, which usually begins within 1 hr. after the injection of endotoxin and persists for 2 to 4 hr. As pointed out in a preceding section, this may in part result from sequestration of leucocytes in the capillaries of visceral organs. An increased adhesiveness of the cells, with intravascular clumping, may contribute to the event, and may actually be the underlying cause.

The third change occurs during the period of leucopenia. Stetson (77), in a histological study of the prepared skin at various intervals following the provoking injection, found that many of the small venules and capillaries became occluded by "plugs" of leucocyte-platelet aggregates which filled the entire lumen and extended along the vessels in the form of thrombi. This event occurred before there was any evidence of necrosis or hemorrhage in the surrounding tissues, but was soon followed by necrobiosis involving all cellular components in the prepared area.

The fourth, and final change consists of a generalized dilatation of vessels throughout the prepared skin, which is accompanied by disappearance of most of the leucocyte-platelet thrombi (as judged by histological sections) and by hemorrhage into the damaged tissues.

An entirely similar sequence of events was observed by Stetson (77) in prepared skin during provocation of the Schwartzman reaction by intravenous injection of crude preparations of rabbit liver glycogen. Here, however, there was a difference in the rate of progress of the reaction. It is known that glycogen suspensions, and also a number of other particulate and colloidal materials, have the property of provoking the local Schwartzman reaction (5, 61, 111), and with such materials the reaction develops much more

rapidly than with intravenous endotoxin. It is common to observe hemorrhage occurring within 30 min. after an injection of glycogen, in contrast to the 3 hr. usually required with endotoxin. In this circumstance, Stetson (77) found that leucopenia also occurred much sooner (often within 15 min.), and leucocyte-platelet thrombi were demonstrable before the appearance of hemorrhage.

These observations provide a mechanism which can account for an important part of the process of provocation of the local Shwartzman reaction. The reasons for the particular vulnerability of prepared skin tissue to the accumulation of these transient cellular thrombi, and for the development of hemorrhagic necrosis following this degree of ischemia (which one would not expect to cause so drastic a response), must be sought in more indirect evidence. It is possible that prepared skin may be especially endangered by degrees of anoxia which would not affect normal tissue, because of the abnormal increase in the formation and accumulation of lactic acid in the area. Cessation of blood supply in such a tissue would result in a rapid lowering of redox potential, with damage to vessel walls and other structures occurring as a direct result, or indirectly as the result of proteolysis (61).

An additional mechanism, known to be brought into play by endotoxin, may be of great importance in provocation of the local reaction. The intense, generalized arteriolar constriction described by Delaunay and associates (6) causes a marked degree of capillary and venular stasis for long intervals, and this may be a determining factor in the fixation and augmentation of cellular aggregates within these vessels. The effect of adrenergic blocking agents on the Shwartzman reaction has not been reported. These substances are difficult to study in rabbits, because of the high degree of resistance which is present in this species (112). An observation recently made by Stetson (113) is of some interest: Infiltration with epinephrine of the tissues surrounding a prepared skin site was followed by hemorrhagic necrosis resembling a typical Shwartzman reaction; no lesions occurred after similar treatment of normal skin.

Two items of indirect evidence concerning the role of leucocytes and of thrombosis, respectively, must be mentioned. Inhibition of the reaction by nitrogen mustard (114) was shown by Stetson & Good (115) to be directly correlated with the leucopenia-producing effect of this drug. Heparin, when given in anticoagulant doses at the time of provocation, was found to prevent completely the local Shwartzman reaction by Good & Thomas (116), and Cluff & Berthrong (117). Whether heparin acts in the situation as an anticoagulant, preventing the establishment of cellular thrombi *in situ*, or in some other manner remains unsettled. However, Good (118) has recently demonstrated prevention by a synthetic dicoumarin-like anticoagulant (Tromexan).

*The generalized Shwartzman reaction.*—This reaction occurs when both the preparing and provoking injections of endotoxin are given by vein, and

consists of extensive lesions of hemorrhagic necrosis in many internal organs. The most characteristic lesion, and the one which identifies the reaction as such, is bilateral cortical necrosis of the kidneys (5, 7, 8, 9).

There are certain striking similarities between this and the local reaction. In both, the presence of polymorphonuclear leucocytes is apparently necessary, as indicated by inhibition of both by nitrogen mustard, and the correlation of inhibition with the leucopenia caused by mustard (7). Heparin inhibits both reactions (116). The basic change in the pathogenesis of renal cortical necrosis, as in the dermal Schwartzman reaction, is occlusion of small blood vessels. But here an important difference appears: the material which occludes the glomerular capillaries in the earliest stage of the generalized Schwartzman reaction is amorphous, homogeneous, and eosinophilic, and bears no resemblance to platelets or leucocytes or their fragments. Its nature is unknown; in its staining properties it resembles fibrin, or fibrinoid (7, 51). Moreover, this material does not appear, nor does renal necrosis occur, when glycogen or other nonbacterial materials capable of provoking the local skin reaction are used in attempts to provoke the generalized Schwartzman reaction (7).

There does not seem to be any morphological basis for an analogy between the state of preparation for the local Schwartzman reaction and the situation in the animal prepared for the generalized reaction. There is no inflammation in the kidney at this time, nor are abnormal accumulations of polymorphonuclear leucocytes to be found in any tissue. It may be that the preparatory intravenous injection of endotoxin, in the generalized reaction, serves a function which is altogether different from that of the skin injection in the local reaction. Indeed, there is reason to believe that the preparatory intravenous injection may exert its effect not in the kidney, but in the unidentified system which is responsible for the animal's innate resistance against endotoxin.

Beeson (97) showed that animals with induced resistance against the pyrogenic effect of endotoxin were also resistant to the local Schwartzman reaction and that the state of resistance was eliminated when Thorotrast or trypan blue were injected before the provoking injection of endotoxin. Good, Smith & Thomas (104, 105) found that these colloidal substances, as well as colloidal iron and carbon suspensions, had an analogous effect on the resistance of normal animals. When toxin was injected intravenously, after an injection of one of the materials, the animals exhibited a greatly enhanced susceptibility to the lethal effect and developed the typical renal lesion of the generalized Schwartzman reaction. Pretreatment with cortisone before an injection of endotoxin had a similar effect (51).

The mechanism of resistance to the necrotizing action of endotoxin has been attributed to a function of the reticuloendothelial ("R.E.") system, on the basis of these observations (97, 51). There is some danger of oversimplification in the use of a term such as "R.E." to apply to the functions of a mechanism as complex and ill-understood as the one which is involved in

the clearance of foreign colloidal substances from the blood. The changes which must occur within the circulating blood, after the introduction of such materials as Thorotrast, may have more significance than the final appearance of metallic aggregates inside the reticuloendothelial cells. The term "blockade," which has been used to designate the alteration in function which occurs after injection of these materials, may have little real meaning as far as the operation of the reticuloendothelial cells themselves is concerned. But the existence of a system of functions other than cellular, having to do with "coating" of foreign materials in the circulating blood, for example, or with transport of the materials via the blood to particular tissue sites, may be of great importance in the disposition of endotoxins. Whatever its real nature may be, there seems to exist, in the normal animal, a device which serves as protection against the necrotizing effects of endotoxin revealed in the generalized Schwartzman reaction, and which is subject to experimental manipulation and study. Investigation of this mechanism may contribute to an understanding of the biological properties of endotoxins, and, at the same time, light up the contours of the mechanism itself.

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